This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

+ *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.

+ *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.

+ *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.

+ *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at `http://books.google.com/`

LANE MEDICAL LIBRARY STANFORD
L648 .L61m 1922 STOR
Endocrine glands and the sympathetic sys
24503423935

LANE
MEDICAL LIBRARY
SEAL OF THE LELAND STANFORD JUNIOR UNIVERSITY
SEMPER VIRENS
1885
HENRY LEE DODGE MEMORIAL

ENDOCRINE GLANDS
AND
THE SYMPATHETIC SYSTEM

BY

P. LEREBOULLET : P. HARVIER : H. CARRION
A. G. GUILLAUME

TRANSLATED BY

F. RAOUL MASON, M.D.

INSTRUCTOR IN PEDIATRICS NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL; ASSISTANT
ATTENDING PHYSICIAN WILLARD PARKER HOSPITAL; ASSISTANT PEDIATRIST NEW YORK
POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL OUT-PATIENT DEPARTMENT
ASSISTANT ATTENDING PHYSICIAN, BABIES' WARD, NEW YORK POST
GRADUATE MEDICAL SCHOOL AND HOSPITAL.

WITH THE COLLABORATION OF

DANIEL R. AYRES, A.B., M.D.

ASSISTANT PROFESSOR OF GYNECOLOGY NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL;
ASSISTANT VISITING OBSTETRICIAN CITY HOSPITAL, NEW YORK

PHILADELPHIA & LONDON
J. B. LIPPINCOTT COMPANY

LANE LIBRARY

COPYRIGHT, 1922, BY J. B. LIPPINCOTT COMPANY

PRINTED BY J. B. LIPPINCOTT COMPANY
AT THE WASHINGTON SQUARE PRESS
PHILADELPHIA, U. S. A.

L640
L61iw
1922

PREFACE TO THE AMERICAN EDITION

There is no subject in medicine at the present time which has aroused such a widespread interest as endocrinology. The reason for this is obvious. In practically every specialty, be it internal medicine, surgery, gynecology, neurology or pediatrics, our knowledge of this subject is increasing daily and finding new applications.

At first our use of the endocrines was limited to such applications as thyroid in cretinism, or pituitrin to stimulate labor pains. We now know that there are numerous grades and varieties of disturbances of the glands of internal secretion giving rise to many troublesome symptoms and pathological conditions, which could not very well be relieved by our common therapeutic measures. Many of these conditions are now amenable to treatment by means of glandular extracts. A few examples are sufficient to illustrate this: The improvement of certain persistent cases of enuresis or what at one time seemed to be ordinary cases of epilepsy by means of pituitrin; the relief of asthenia following acute infections by the administration of suprarenalin; the benefit derived from thyroid, thymus, pituitary or ovarian extracts in gynecological conditions; the variety of obscure skin conditions which have been cleared up by giving one or more of the glandular extracts, and many more could be added to this list.

The remarkable feature of this method of treatment is that it can be both symptomatic and curative in its action. This does not mean of course that all body ailments can be treated by the administration of glandular extracts, but a great many can be helped. An understanding of

53051

the subject is necessary and, as in other phases of medicine a proper diagnosis is important.

We are all liable to become rather confused by the mass of new evidence brought forward constantly as well as by the extravagant claims of certain enthusiasts.

The French have probably as a nation been more interested in endocrinology than any other people and the names of Claude Bernard, Brown-Sequard, Charcot and, more recently, Pierre Marie and Sergent are closely related to the history of this subject.

The translator believes that the writers have condensed in this volume in a clear and sober manner our present-day knowledge of the endocrines without the addition of any fanciful theories. Very appropriately, the study of the sympathetic system has been included, as these two subjects are closely connected. While at first the study of the sympathetic system may seem rather tedious, the reader will be amply repaid for his effort, as this subject, on which so little has been written, enables us to gain a better understanding of functional pathology.

At the request of the authors this translation has adhered, as far as possible, to the original French text. When it seemed suitable, footnotes have been added with the collaboration of Dr. Ayres. Certain recent facts have been omitted as not having as yet been sufficiently controlled by unprejudiced observers. For instance, the lack of small quantities of iodine in the water or food supply as the probable etiological factor in colloidal goitre, or the selective action of quinine or its derivatives on the true sympathetic and its clinical application in certain cases of tachycardia.

The translator wishes to express his thanks to the publishers who have made this American edition possible.

F. Raoul Mason.

CONTENTS

INTRODUCTION

GENERAL CONSIDERATIONS ON THE ENDOCRINE GLANDS AND THEIR PATHOLOGY.

P. Lereboullet

PAGE

I. NORMAL AND PATHOLOGICAL ANATOMY AND PHYSIOLOGY OF THE ENDOCRINE GLANDS 4
  What are the endocrine glands for 4
  Ways of studying and classifying the products of internal secretion 8
  Functional disturbances. (Insufficiency, hyperfunction, aberration of function, functional glandular corrolation. Part played by the sympathetic) 16
II. THE CLINICAL ENDOCRINE SYNDROMES 25
III. GENERAL THERAPY OF DISEASE OF THE ENDOCRINES 40
  Etiological treatment 42
  Surgical treatment 43
  Treatment with X-ray 45
  Organo therapy 47

PATHOLOGY OF THE ENDOCRINE GLANDS

P. Harvier

I. PATHOLOGY OF THE THYROID 57
  Functions of the thyroid 57
I. THYROID INSUFFICIENCY SYNDROMES 60
  Adult myxedema 60
  Myxedema in childhood 63
  Post operative myxedema 66
  Endemic myxedema or cretinism 67
  Abortive myxedema (chronic mild hypothyroidism, slight thyroid insufficiency) 67
  Treatment of myxedema and of thyroid insufficiency 71
II. THE SYNDROMES OF HYPERFUNCTION OF THE THYROID 75
  Exophthalmic goitre 75
  The various Basedow's disease syndromes 89
  Hyperthyroidism simulating Basedow's disease 91
  Treatment of exophthalmic goitre and Hyperthyroidism 92
  Thyroid instability 96
  Acute thyroiditis. Tuberculosis and syphilis of the thyroid 97

PAGE
II. PATHOLOGY OF THE PARATHYROID GLANDS 102
Functions of the parathyroids 102
Parathyroid syndromes 103
Parathyroid insufficiency and tetany 103
Possible parathyroid syndromes 115
Sudden death in children and lesions of the parathyroids 116
III. PATHOLOGY OF THE THYMUS 117
Functions of the thymus 117
Thymic syndromes 119
Syndromes of thymic hyperplasia 119
Hypertrophy of the thymus 120
Sudden death of thymic origin 123
Hypertrophy of the thymus in diseases of the endocrines 126
Symptoms of aplasia of the thymus. Congenital thymic idiocy 127

PATHOLOGY OF THE ADRENALS

Functions of the adrenal glands 128
I. SYNDROMES OF ADRENAL INSUFFICIENCY 131
Adrenal insufficiency 132
Addison's disease 143
Mild adrenal insufficiency 152
II. SYNDROMES OF HYPERFUNCTION OF THE ADRENALS 156
III. ADRENAL TUMORS AND DYSTROPHIES OF ADRENAL ORIGIN 161
Genito-adrenal syndrome 162

PATHOLOGY OF THE PITUITARY

Functions of the pituitary 170
Pituitary Syndromes 172
Acromegalia 172
Gigantism 178
Pituitary infantilism 183
Adiposo-genitalis syndrome 185
Pituitary glycosuria 188
Pituitary polyuria 190
Pituitary syndromes and tumors of the pituitary 191
Abortive pituitary syndromes 196
Pituitary syndromes in infections 197
Treatment of pituitary syndromes 197

PATHOLOGY OF THE PINEAL GLAND

Pineal syndrome 201

PATHOLOGY OF THE TESTICLES

Functions of the testicles 208
I. SYNDROMES OF TESTICULAR INSUFFICIENCY 212
Castration 212

PAGE

PATHOLOGY OF THE TESTICLES—*Continued*

Undescended testicles 214
Testicular insufficiency due to toxic or infectious lesions of the testicles 215
II. SYNDROMES OF HYPERORCHIDIA 218
Indications for testicular organo therapy 220

PATHOLOGY OF THE OVARIES

Functions of the ovaries 221
SYNDROMES OF OVARIAN INSUFFICIENCY 223
Post operative ovarian insufficiency 223
Disturbances of the normal menopause 227
Congenital ovarian insufficiency 228
Ovarian insufficiency at puberty 228
Acquired ovarian insufficiency 229
Thyroid ovarian insufficiency 230
Treatment of ovarian insufficiency 231
SYNDROMES OF OVARIAN HYPERFUNCTION 233
Metrorrhagia of puberty 234
Metrorrhagia of the menopause 234
Treatment of ovarian hyperfunction 236

PATHOLOGY OF THE MAMMARY GLAND

Mammary hypertrophy at puberty in women 239
Mammary hypertrophy in man 241
PLURIGLANDULAR SYNDROMES 243

PATHOLOGY OF THE SYMPATHETIC SYSTEM

Part I.

INTRODUCTION TO THE STUDY OF THE NERVOUS SYSTEM OF VEGETATIVE LIFE FROM AN ANATOMICAL AND PHYSIOLOGICAL POINT OF VIEW.

A. C. Guillaume.

The sympathetic, cranio pelvic system, autonomic system, endocrine glands.

I. WHAT DO WE MEAN BY THE SYMPATHETIC SYSTEM 254
II. THE ANATOMICAL VEGETATIVE NERVOUS UNITY 263
III. THE COMPONENTS OF THESE SYSTEMS 274
IV. ANATOMICAL AND PHYSIOLOGICAL DESCRIPTION OF THE VARIOUS ELEMENTS 286
V. PHYSIO PHARMACOLOGICAL OPPOSITION OF THE TWO GREAT VEGETATIVE SYSTEMS 306

PAGE

PATHOLOGY OF THE GREATER SYMPATHETIC

P. HARVIER

PART II.

I. HYPEREXCITABILITY SYNDROME OF THE VEGETATIVE NERVOUS SYSTEM ... 315
(SYMPATHICOTONIA AND PARASYMPATHICOTONIA OR VAGOTONIA)
II. REACTION OF THE VEGETATIVE NERVOUS SYSTEM IN THE COURSE OF DISEASE AND VISCERAL AFFECTIONS ... 319
III. ENDOCRINE SYMPATHETIC SYNDROME ... 324
IV. LOCALIZED SYMPATHETIC SYNDROMES ... 328
Cervical sympathetic syndromes ... 328
Mediastinal sympathetic syndrome ... 335
Abdominal sympathetic syndrome ... 337

ORGANO THERAPY

H. CARRION

PHARMACOLOGICAL FACTS.

Physiological basis of organc therapy ... 349
Modes of action of organo therapy ... 351
The preparation of the various products used in organo therapy ... 357
The administration of organo therapeutic products ... 360
General indications for organo therapy ... 361
Contraindications to organo therapy ... 362
Technique of organo therapy ... 363
Doses of organo therapeutic products ... 364
Certain generalities on the chief organo therapeutic products ... 365

INTRODUCTION

GENERAL CONSIDERATIONS ON THE ENDOCRINE GLANDS AND THEIR PATHOLOGY.

By P. LEREBOULLET
"Agregé" Professor of the faculty of medicine of Paris.
Physician to the hospital for sick children.

ENDOCRINE GLANDS
AND
THE SYMPATHETIC SYSTEM

INTRODUCTION

The importance of the endocrine glands, both in physiology and pathology becomes every day more evident. By means of anatomical and experimental researches on the one hand, and, from clinical, as well as therapeutical observations, on the other, it is possible to realize the primordial importance of these glands, however complex it may appear, and sufficient knowledge has been obtained to reach some practical medical conclusions.

These are the conclusions which Dr. Harvier has reviewed in this volume. In a series of clear and concise chapters he has brought up to date our knowledge of the endocrine glands and their pathology. Very rightly abstaining from all hazardous pathogenic theories, he has limited himself to review the various glands and after going over their physiological action, has described their functional disturbances and the diseases resulting from these alterations.

Before going over these analytical chapters it would perhaps not be amiss if we reviewed the trend of thought which at the present time directs the medical mind in the observation of endocrine pathology and described how our knowledge on the subject has slowly developed from the anatomical, physiological, clinical and therapeutical point of view.

1. NORMAL AND PATHOLOGICAL ANATOMY AND PHYSIOLOGY OF THE ENDOCRINE GLANDS.

WHAT ARE THE ENDOCRINE GLANDS?

They are the glands which pour out their secretions, not in extraneous places, like the cutaneous surface of the gastro intestinal tract, but in the body itself, that is, in the blood stream. The notion that such glands existed (internal secretions), as opposed to the glands of external secretion has only been reached very slowly and it has nearly always been French scientists which have led the way.

The founders of the theory of internal secretions were, Claude Bernard and Brown-Sequard. As has been shown by Gley, they had predecessors like Legallois and Bordeu. It was Claude Bernard in 1855 who discovered the glycogenic function of the liver and who in this way placed the physiology of internal secretions on a firm foundation.

In a series of investigations, between 1855 and 1867 he admitted that "the secretory cell attracts, creates, elaborates in itself secretions which it pours out, either on the outside on the mucous membranes or directly into the blood stream. I have called those which are poured on the outside *external secretions* and those which are poured into the organism itself *internal secretions*. The internal secretions are not as well known as the external secretions. I believe, however, that they definitely exist and we must consider the blood as the product of vascular blood organs. The glycogenic liver is a large blood organ, that is, a gland which has no external opening. From this organ arises the various sugar products found in the blood and perhaps certain albuminoid substances. There are, however, other blood organs such as, the spleen, the thyroid, the suprarenal capsules, the lymphatic glands, the function of which is not yet determined. However, these glands should be considered as playing a part in the regeneration of the blood plasma as well as in the formation of white and red cells which float in this liquid." The idea of internal secretions was clearly seen by Claude Bernard, but in his mind they were always limited to the composition of the blood and did not have the multiple conceptions we have of these to-day in modern physiology. For a long time the findings of Claude Bernard failed to make any impression on his contemporaries and they were not likened to those of Brown-Sequard on the physiology of the suprarenal capsules and the death of animals which had these capsules removed (1856) or to the work of Vulpin on the coloring matter of the medullary part of the suprarenal capsules (1856) and its passage into the suprarenal veins, or to the work of Schiff on the relations of the spleen with the digestive functions of the pancreas. When Schiff in 1884 published his experiments on the effect of the removal of the thyroid in animals researches resulting from the work of the two surgeons, Reverdin and Kocher, on post-operative myxedema, he did not think of the possibility of internal secretions as established by Claude Bernard.

It was Brown-Sequard in 1889 in his investigations of the therapeutic action of testicular fluid who understood the full value of the theory of internal secretions and who founded endocrinology. His original researches can possibly be criticized ; they, however, contain the germ of all the ideas which have been used as a starting point on all the studies carried out during the last thirty years on internal secretions. While taking up again the idea of Claude Bernard on the action of glands without external secretions on the composition of the blood he showed that many organs secrete in the blood certain substances which have the ability to act selectively on certain organs, be they near or far away. "Each tissue and more generally each cell of the organism secretes of itself special products, or ferments, which are poured into the blood and which influence through the intermediary of this liquid, all the other cells, thus brought in contact with each other by a mechanism other than the nervous system." From this was born the idea of the action on various organs of specific substances secreted in the blood and as a corollary this other fundamental notion of a functional corollation of the secretions. The subsequent researches of Brown-Sequard and of a number of physiologists and physicians showed, in spite of the poor result of testicular fluid, how valuable were these theories. Not only did it open a new path to experimental physiology, but it allowed new clinical interpretations and new therapeutic methods.

Pathology very quickly came to the help of physiology and shed considerable light on the endocrine glands. The thyroid gland is the best known in this respect. The conception of myxedema was born from the observation of Gull, Ord and Charcot on senile myxedema, of Reverdin and Kocher on post operative myxedema, of Bourneville on idiocy due to myxedema and infantile myxedema, and was made more comprehensive by the investigations of Vassale and Gley who caused the improvement of the severe symptoms resulting from the removal of the thyroid by means of injections of thyroid extracts, and completed by those of Murray applying this method to the treatment of human myxedema. In this way the double conception that an insufficiency of the thyroid was responsible for this condition and it could be remedied by means of organotherapy was the result of the discoveries of Brown-Sequard.

Shortly afterward the researches of Moussu and those of Gley on the parathyroid glands and the part they play in the production of tetany opened up a new chapter. A few years ago Morel in physiology and Harvier from an anatomical and clinical point of view brought this subject up to date.

The suprarenal gland, of which already in 1856, Brown-Sequard had had a glimpse of its importance, is another example of the progress of endocrinology. The anatomical and clinical investigations of Addison's disease had already shown the consequences of its insufficiency. Oliver and Schafer, Cybilski and Langlois showed the cardio-vascular action of the suprarenal extract and of the venous blood from the suprarenal gland. These researches were finally vindicated by the discovery of suprarenalin, the product of the secretions of this gland. Its hypertensive action has led to many important conclusions. We know the part which Josue applies to a hypersecretion of suprarenalin in the production of suprarenal atheroma. As has been pointed out by Sergent and many other clinicians, the part played by an insufficiency of the suprarenals in acute and chronic affections has been determined, in those cases in which hypotension is a cardinal sign. The use of suprarenal extract has been considerably increased since these facts have been brought forward. If certain restrictions have been made by Gley from the point of view of physiology, the facts determined clinically and therapeutically still remain true.

The story of the investigation of the pancreas is just as rich in useful informations. In 1889-1890 Mering and Minkowski proved experimentally the part played by alterations of the pancreas in the etiology of diabetes, already clarified clinically by Lancereaux and it was shortly afterward that verifying and confirming this discovery, R. Lepine, Thiroloix and Hedon showed that in this case we were also dealing with an internal secretion of the pancreas.

Shortly afterward the pathology of the pituitary gave a new example of the physiology and pathology of an internal secretion. The discovery of acromegalia by Pierre Marie was the first chapter of this pathology, which was made more complete by the study of gigantism, infantilism, certain adiposogenital syndromes and diabetes insipidus. The remarkable investigations of Harvey Cushing have helped to clarify the subject, both clinically and experimentally. We must, however, accept with reserve some of the facts, as it is possible that some of his theories may not be confirmed. The pituitary has become one of the most important and most interesting organs among the endocrine glands. From a therapeutic point of view pituitary organo therapy has been very effective, just as much as a symptomatic medication as in the case of substitute medication. The results are comparable to those obtained in thyroid administration.

These rapid historical considerations are sufficient to establish the significance of the initial observations of Brown-Sequard. Gradually, thanks to the parallel help of pathology and physiology, the notion of endocrinology has become more definite and this subject has now a justifiable place in the field of medicine.

WAYS OF STUDYING AND CLASSIFYING THE PRODUCTS OF INTERNAL SECRETION.

It is not sufficient to just say that the vascular blood glands have an internal secretion which have a part in the formation of the blood and act on other structures and organs. It is necessary to prove the reality of these secretions, by studying histologically the secretory function of the cells, determine chemically the nature of the substance secreted, and what is more important, by means of physiological and experimental studies prove the action of these secretions. By these means is constituted a solid base for physiological, pathological and clinical deductions. In this respect considerable progress has been made during the last few years, but there is still much to be done. The study of the pathological gland goes parallel with the study of the normal gland. The thyroid and the suprarenal are the best known from the histological and physiological point of view. They are also the two glands, among those of internal secretions, whose pathology is most definite. We are beginning to know the pituitary as regards to its histology and physiology and it is only since then that its pathology is better understood. It is to be hoped that further studies of the physiology and anatomy of the endocrines will be made, which will throw further light on their pathology. Already certain well-defined facts have been established.

The Histological Study of these glands has enabled us to examine how the glands work. Not only can we study the thyroid vesicles, for instance, and see how the gland secretes a colloidal substance, which is re-absorbed by the blood vessels surrounding the epithelum but we can, thanks to the modern methods, delicately stain the cellular protoplasm and see the glandular cell in activity. In the case of the liver, fill with glycogen, or suprarenalin, in the case of the medullary cells of the suprarenal capsule. In this respect, the researches of Henle are very suggestive. He has opposed the chromaffin, or suprarenalin cells to the cells with collesterin or nerve cells. Very significant are also the histological investigations on the acidophils, basophils, cyanophils, chromophobes cells of the pituitary, notably the work done on the pars intermedia, at the junction of the anterior and posterior lobe. Where the colloidal glandular secretion accumulates and which allows us, if not to understand, at least to imagine what can be the function of this vascular nervous gland (Soyer). Histology is all the time bringing us new findings which can be utilized by the physician. By understanding the cellular mechanism of the endocrin secretions, it is possible to better understand the functional disturbances noticed clinically. It is thanks to histology, that by the microscopic study of the lesions of exophthalmicgoitreit is possible to invoke dysthyroidism as the cause of the symptoms and not a simple hyperfunction.

THE CHEMICAL STUDY by determining in these substances, certain definite compounds, such as, suprarenalin, glycogen, cholesterin, etc., takes us one step further in the study of the glandular secretions. While we do not deny the progress made in this line during the last few years, we must admit that there is still much to be learned in this respect. How could it be otherwise, considering the complexity of the study of these secretions which can only be found either in the blood or in the cell itself as contrasted with the products of the glands of external secretion. It is this lack of chemical knowledge which makes our treatment with organo therapeutic products so empirical. We know the action of the total extract; sometimes we know the action of certain of the constituents, such as, suprarenalin, but in the majority of cases the pharmacological study of the extract is impossible. In this respect it is extraordinary how the thyroid secretions, so well known in their therapeutic effects, are so ill defined from a chemical point of view. It is to be hoped that the rapid progress of chemistry will soon overcome this deficiency. Already we know something of the secretion of the anterior lobe of the pituitary (tetheline), showing the part played by certain liquids of endocrine origin and the possibility of their use in therapeutics (Brailsford Robertson).

THE PHYSIOLOGICAL STUDY of the internal secretions gives us much more definite knowledge than either histology or chemistry, but without these two it must remain incomplete. We are able to study from it the specific action of substances extracted from a gland or from a vein afferent from this organ. By this method it has been possible to study the character of the venous blood of the suprarenals and obtain the characteristic cardio tonic action. In the majority of cases all that can be done is to study the action of extracts of organs. This is the method which has given the best results and from which organo therapy has been deducted. We must not, however, make statements too specific as regards these. Gley has shown how careful we have to be. The isolation of extracts of organs is always complex. What do these substances represent? Do they exist in the living organ; are they excreted in the venous blood?

If so, are they excreted all at once or in small doses? The action of the extract cannot be the same as that of the blood coming from the veins of the organ and the pathologist must be careful not to make any rash deductions, basing his conclusions on the action of an organic extract and comparing it to certain symptoms noted in certain affections. We must also keep in mind the toxicity of extracts of organs. This toxicity varies according to the method of preparation and can become more important than the specific action of the extract of the organ. It is also probable that the various manipulations which are performed in order to lessen the toxicity, can also modify the action. It is possible that the administration of extracts of organs be followed by anaphylactic phenomena, since these extracts contain foreign proteins or inversely tachyphylaxis, that is, a rapid immunization against the toxic action of certain organs. This last suggestion, to which we are indebted to Champy and Gley, adds to the complexity of investigating the mode of action of extracts of organs. There are certain extracts which will only give a reaction when given in extra physiological doses, the doses used representing the total weight of the organs from which these extracts are obtained. This is the case of pituitrin which is used in relatively large doses and whose efficacious action cannot be contested.

All these facts show how careful we must be in interpreting the therapeutic results obtained, and, as Gley has said, "the real criterion of the function of an internal secretion is the presence of a specific product in the venous blood of a gland." This criterion so far has only rarely been complied with. This does not mean that we must dismiss all the facts revealed by therapy and experimental investigations on the extracts of these organs. It simply means that we must be very critical and not jump at conclusions.

Experimentation on Animals often have confirmed the observations obtained with the extracts. All that is necessary is to recall the results of experimental thyroidectomy and para thyroidectomy, of hypophysectomy, and castration to establish the fact that these glands play a physiological part in the organism and that alterations in these glands will result in pathological conditions, which we run across clinically.

The Nature of These Secretions is still uncertain. It was admitted early by Gley and others that these glands produced substances having a specific action on other glands or tissues; iodothyrin for instance, which is secreted by the thyroid, has a direct action on metabolism, and its absence will cause disturbances in nutrition. These substances of glandular origin, having a specific stimulating action have been called functional stimulants and were termed *hormones* by Starling in 1905. It is by the intermediary of these hormones that the functional corollation of chemical origin which was suspected by Claude Bernard, is accomplished, as differentiated from corollation of nervous origin, which has been known for a long time. But simply to know of the existence of hormones does not mean that we understand them well. The duodenal secretin stimulating the pancreas is a certain type of hormone, the suprarenalin, a product of the chromaffin cells of the suprarenals and other cells, has a stimulating act on the cardio vascular system and represent another type of hormone. It is also possible that iodothyrin really exists, although not isolated definitely and that it may have a stimulating metabolic effect on connective tissue. It is possible that there are other hormones of endocrin origin, but so far we know very little about them.

Next to hormones, the endocrine glands secrete substances which are not cellular stimulants but materials which they utilize. Glycogen of hepatic origin, the fats, are examples of nutritive substances utilized in the formation of energy. Other substances must be used in the repair of the blood (specific proteins of the blood). Outside of these, those which are of most interest to the physician are those which help in the building up of tissues during the course of development of the organism; these are the *morphogenetic substances*. Physiology, anatomy and clinical experience have shown the evidence of glands having a morphogenic action, such as, the interstitial gland of the testicle, the corpus luteum, the thyroid, the pituitary. The substances secreted by these glands have a chemical morphological action, the study of numerous cases of infantilism is sufficient evidence of this. What are these substances? What is their mode of action? We do not know. These are the *harmozones* of Gley. (From the Greek *I regulate, I direct*). The study of growth and its disturbances have been revolutionized by these new ideas and it is to be hoped that in the future our knowledge on this subject will increase considerably. These chemical compounds which regulate development are among those whose action must be most carefully determined in order to use them therapeutically. The action of thyroid and pituitary organo therapy in a great many disturbances of growth shows what may be expected once our knowledge of the harmozones of the thyroid and the pituitary are better known. The recent investigations on the anterior lobe of the pituitary and the regulating action on growth by a substance, *Tetheline*, which can be extracted from this lobe is at least very suggestive (Brailsford Robertson).

The endocrine glands can, therefore, create, either nutritive substances, such as, sugar, hormones, specific cellular stimulants, such as, suprarenalin, harmozones or regulating substances and finally we can, following Gley, separate from the hormones, certain by-products or par hormones, such as, urea, the product of the change of toxic substances like ammonia or amino acids. It is also possible to place next to the hormones, substances which, instead of being stimulating, are depressing. These have been designated by Schafer under the name of *Chalone* (from the Greek *I slow down*). Perhaps this distinction is too absolute; one internal secretion can be, according to the case, either stimulating or depressing.

The conception of the various glands of internal secretion must be well understood before going into the study of their pathology. It shows how complex is the mechanism and how difficult it is to deduct an insufficiency or a hyperfunction from functional alterations. The complexity of the subject is made more pronounced by the fact that a multiple of causes can cause disturbances in the function of the endocrine glands and cause a multiple of secondary syndromes.

These facts which I have just enumerated have enlarged our studies of endocrinology. Instead of limiting ourselves to the glands which were first considered as having only an internal secretion, such as, the thyroid, the pituitary, the adrenals, etc., it has spread to the thymus, to the spleen, the bone marrow which is not a glandular organ, but a blood and lymph forming organ. After all, have not all cells an internal secretion? And has not the adipose cell of connective tissue certain characteristics of a gland of internal secretion? The custom, however, is to limit the study of internal secretion pathology and physiology to certain glands and this custom is justifiable. For instance, in spite of the latest investigations on the liver, these have not been included in this volume, nor the relationship between disturbances of bone marrow and certain dystrophies (Hutinel). These do not belong to this subject. The glands which are studied from a functional and pathological point of view belong to a certain group having anatomical and physiological connections with the sympathetic, so that the study of sympathetic and its disturbances follows naturally that of the endocrine glands.

It is not planned in this work to give the physiological history of these glands or to describe their histology or even to analyze their actions in detail. The aim is simply to describe some of their normal and pathological functions. Some of them have a double secretion, internal and external, like the pancreas, the ovary and the testicle. Others have only one secretion, such as, the thyroid, the adrenals and finally, there are some whose secretions are still not well understood, such as, the pituitary, the parathyroid, etc. Gradually our knowledge of all these glands has become broader and at the present time it is possible to give a fairly accurate description of their pathology and to give some general principle as to treatment.

FUNCTIONAL DISTURBANCES.

Insufficiency. Hyperfunction. Aberration of Function. Functional Glandular Corrolation. Part Played by the Sympathetic.

The destructive lesions being the easiest ones to interpret and the resulting conditions the easiest to appreciate and reproduce experimentally by the removal of the organ, it was the functional insufficiency of an organ which was first noticed. Insufficiency of the thyroid was spoken of when myxedema followed the removal of the thyroid, insufficiency of the adrenals when the destruction of the adrenals was noticed in Addison's disease. Inversely it was noticed that in some cases there seemed to be exaggeration of function and that the symptoms noticed were the inverse of those observed in insufficiency. These cases were spoken of as hyperfunction; hyperfunction of the thyroid was opposed to hypothyroidism of myxedema, hyperfunction of the adrenals was suspected as a cause of hypertension, and inversely hypotension was suspected to be due to hypoadrenalism. Gradually it was found out, after many physiological and anatomical observations, that functional disturbances are not always as simple and aberration of function had to be added to the others.

From a descriptive point of view it is very useful to make such a division. As soon as an endocrine gland is disturbed its function is altered, either there is an excess, a decrease or an aberration of the secretion; that is, in the case of the thyroid, hyperthyroidism, hypothyroidism, dysthyroidism. It is easy to see that the analysis of these disturbances is useful, even necessary in thyroidien organo therapy, efficacious in hypothyroidism, possibly detrimental in hyperthyroidism, and in case of dysthyroidism some other therapeutic measure may be indicated. However, it is wise to avoid too rigid a classification. As the facts become better known, the notion of aberration of function becomes more important than pure hypo or hyperfunction. From a physiological point of view, Gley has recently shown what facts we have to meet when we speak of a simple functional insufficiency; for instance, when it is known how small a portion of thyroid or pancreas it is essential to leave to prevent the accidents resulting from the total removal. Hypofunction has often been implicated without any demonstrable reason, even in cases where the alteration of the gland, the adrenal, for instance, would seem to result in a secretory deficiency. It has been demonstrated how small the quantity of suprarenalin secreted was to keep up the muscular tone, the researches of R. Porak, both clinical and experimental are very suggestive from this point of view. The reality of insufficiencies is, however, not in doubt, but they are possibly associated with other functional disturbances and other physiological modifications which seem to make their results more pronounced.

Hyperfunction, associated with an endocrine hypersecretion, is more difficult to prove. Hyperfunction has been admitted to exist, basing ourselves on clinical and therapeutical facts, but has never been reproduced experimentally. The repeated injections of pituitrin have never caused the appearance of the symptoms of acromeglia; in the same way, a true increase in the secretion of suprarenalin, in cases of arterial hypertension, has never been proved, and physiologically it is hard to conceive of suprarenalin being in the blood in excessive quantity without being destroyed and that a morbid syndrome would result from it. Two examples in endocrine pathology will do more to explain this than anything else. Exophthalmic goitre was for a long time considered as a manifestation of hyperthyroidism and opposed to myxedema. Facts have, however, been published making the interpretation for the first of hyperthyroidism and the second of myxedema very difficult. Since exophthalmic goitre has been studied more closely and that the lesions have been more carefully investigated it has been recognized by Roussy and others, that therapeutic hyperthyroidism could not be compared to true Basedow's disease and that the latter was a manifestation of dyshypertrophy of the thyroid, that is, an exaggerated and abnormal thyroid secretion. This idea is certainly the clearest of our present knowledge on the subject. In the same way, acromegalia has been considered by some to be a manifestation of hyperfunction. It is relatively frequent to see patients suffering from adiposo genitalis of the adult, (which has been blamed, not without reason, to an insufficiency of the pituitary) show evidences of acromegalia. I have personally seen two cases of this type. The possibility of a dyshyperplasia of the pituitary is best adapted to the facts and would explain the presence of some symptoms due to a functional deficiency with those of hyperfunction. The more we understand the syndromes associated with alterations of the endocrine glands, the more we see the complexity of their functional disturbances. Does this fact not also hold in disturbances of the liver and the kidney, which cannot all be brought back to an insufficiency or a hyperfunction? It is, nevertheless necessary, be it only from a didactic point of view, to look at them from the triple point of view of insufficiency, hyperfunction and aberration of function. Therapy brings other arguments in favor of this classification and it is quite certain that organo therapy by modifying certain disturbances, in leaving alone or exaggerating others, can bring out a glandular insufficiency or inversely, a normal or exaggerated function. While still keeping in mind the importance of functional deviation it is always essential to determine if the symptoms observed in a patient are due to an insufficiency or are secondary to an excessive function. The classification followed by Dr. Harvier in the following chapters is a necessity, but it is well to understand that it is not absolute.

* * * * *

Endocrine pathology appeared at first to be very simple; a certain gland seemed to be responsible for certain symptoms: myxedema was a manifestation of the alteration of one gland only, the thyroid, Addison's disease was due to changes in the adrenals and it was not necessary to invoke other endocrine lesions, acromegalia was due to a lesion of the pituitary. If this had been so in every case, the analysis of functional endocrine disturbances would have been easy. The notion of *functional glandular corrolation*, however, carried out through the blood stream or through the nervous system has complicated matters. The study of infantilism allows us to understand the consequences of this fact. I have previously referred among the endocrine secretions, to the presence of harmozones or morphogenetic substances regulating growth. After the first investigations on hypothyroidism and the observations of Brissaud and Hertoghe, it seemed as if these substances came directly or indirectly from the thyroid and that modifications of these substances were the cause of most cases of lack of growth. Infantilism seemed to be due to hypothyroidism.

It had, however, been previously shown that castration in man and in animals caused certain changes in the development of the skeleton, thus showing the influence of the genital glands. More recently this action was strikingly demonstrated by the influence of the pituitary in certain cases of infantilism, without there being any evidence of any thyroid disturbance. In studying thyroid or pituitary infantilism it was discovered that this was probably due to alterations of the sexual glands. It would seem, therefore, that it was an alteration of the pituitary or of the thyroid, which caused a disturbance of function of other glands (the genital glands), resulting in infantilism; the expression, not of the disturbance of one gland only, but of a multitude of glands. We can sometimes wonder if there is not a pre-existence of an endocrine disturbance on another gland, if the initial alteration of this gland does not represent the whole evolution. It seems to be the case in the facts described by Gandy under the name of *reversive infantilism* and by Brissaud and Bauer under the name of *late infantilism of adults*; sometimes of thyroid, sometimes of pituitary origin. These cases are relatively numerous and the course of the lesions can be clearly followed; in those which I have observed, I have seen quite clearly the appearance of the pituitary lesion, with characteristic symptoms, notably ocular disturbances, and secondarily genital alterations followed by obesity and other changes.

These facts, when the symptomatology is reconstructed, show the simultaneous existence of lesions of several endocrine glands. It is thus in a good many cases of senilism, of gerodermia, genito-dystrophy, etc. It is particularly so in the very interesting cases analyzed by Claude, Gougerous and Sourdel under the name of pluriglandular syndromes. There is no question but that there are cases which clinically and anatomically show alterations of several endocrine glands: adrenal and thyroids, thyroid, pituitary and testicle, etc. A classification based on such changes is, however, difficult to follow.

There are certain conditions, such as, infantilism which I have just referred to, in which the lesion of one gland, the pituitary, for instance, seemed clearly to have preceded that of the other glands. In some cases where the endocrine lesions occur simultaneously, the clinical symptoms are so characteristic that there is no advantage to give it any other name. In other words, the knowledge of a pluriglandular involvement helps us to interpret certain clinical syndromes, and to determine what symptoms belong to such or such a gland and, while keeping to the classical classification, treat these cases by means of mixed organo therapy so as to overcome these various syndromes. This idea helps us to better interpret and treat more efficaciously certain diseases, the nature of which is still rather indefinite. Take for instance, the obesity of the menopause, instead of being entirely dependent on the suppression of the ovarian function, it seems to be due to simultaneous alterations of the thyroid and the pituitary. Dercum's disease is believed to be of thyroid and pituitary origin and the characteristic asthenia associated with this condition is believed to be due to the adrenals. Sclerodermia is not due, as was believed for a time, to thyroid lesions. The adrenals, the pituitary and perhaps the ovary, seem to play a part in some of the symptoms of this disease and mixed organo therapy can do a great deal to relieve the condition. Diabetes often results from the simultaneous alteration of several glands outside of the liver and pancreas. While it is difficult to describe as yet the definite symptoms the pluriglandular syndromes, it is possible in certain well-defined diseases: obesity, diabetes, sclerodermia, genital dystrophy, etc., to bring out the multiple endocrine alterations and to use these facts for the basis of rational medication.

* * * * *

If what I have just said has been understood, the following conclusions result: The functional disturbances resulting from endocrine alterations are complex and only rarely come down to the typical picture of insufficiency or hyperfunction; more often they can only be explained by an aberration of the endocrine secretion, be it exaggerated or deficient, having been modified in its usual characteristics and having a different physiological action. What makes these clinical findings more complicated is the fact that this functional aberration is transmitted by the blood and by the nerves on the function of other glands. In this way the clinical syndromes observed appear as the expression of polyglandular functional disturbances, while originally, due to one gland. The aim of the clinician is to try and determine what are the glandular disturbances in each syndrome and what is their subordination, while an appropriate organo therapy can very usefully modify these symptoms.

One last factor comes into play which modifies the evolution of functional endocrine disturbances; that is the very frequent and very important *disturbances of the sympathetic* in the syndromes under observation. It is impossible to separate the study of the endocrine glands and the study of the sympathetic. It has been known for a long time the part played by it in cardio vascular manifestations, thermic changes, vaso motor, pilo motor changes, etc. . . . . . all manifestations which are indicative to a more or less extensive degree of diseases of the endocrines. It has been known for a long time, for instance, the part played by the stimulation of the sympathetic in Basedow's disease and inversely, the majority of the signs of myxedema have their origin in alterations of the sympathetic, causing a decrease in its activity. Briquet, for instance believes that the chief function of the thyroid is to furnish a necessary stimulant to the sympathetic and a decrease in its function whether total, or partial, causes a decrease in this stimulation, whence myxedema. It is to this same sympathetic that is due the development of bones, growth, puberty, and it is the decrease of its stimulation, by a decrease in secretions from the thyroid, thymus, and other glands, that infantilism, and other disturbances of growth are due to (Briquet). The action of the sympathetic has also been suggested in many other conditions, notably in pigmentation of the skin (chiefly pigmentation due to Addison's disease), in ichthyosis, in sclerodermia which Brissaud has for a long time considered as a disease of the sympathetic system, (be it due or not to endocrine disturbances). In the clinical field, therefore, these few examples are sufficient to show the influence of the sympathetic in the symptoms due to endocrine disturbances. The knowledge of relationship between the two for a long time was rather vague and indefinite. During the last few years anatomists, physiologists and clinicians have attempted to better understand and analyze disturbances of the sympathetic. They have shown how hard it was to dissociate the endocrine from the sympathetic system. An experimental example has been shown in the recent researches of Professor Roger on the relationship between the adrenal glands and the sympathetic, and inversely, the action of the sympathetic on their function. Histologically and embryologically a proof of this relationship has been shown by investigation of the paraganglia. Scattered throughout the abdominal sympathetic they play a complex and important part. They have, just as the adrenal medulla, chromaffin cells which secrete suprarenalin, and in spite of being mixed up with the nervous sympathetic system have, nevertheless, a certain epithelio-glandular nature.

It is also well known that their origin is identical; the original undifferentiated cells become either sympathoblasts, from which arise the sympathetic nerve cells or phæochromoblasts from which originate the adrenal or paraganglionic cells. The neuro chemical corrolation is here very evident, the activity of the paraganglionic cells is closely related to that of the adrenals. Clinically, numerous proofs of the close relationship between the sympathetic and the endocrines exist. Among the most characteristic examples is Basedow's disease, in which the recent researches on disturbances of the sympathetic, by means of the oculo cardiac reflex have given very suggestive results. It has been established, in the course of the study of the endocrines, that adrenalin was sympathicotonic and played an important part in the physiological and pathological function of the nervous system of vegetative life, that adrenal choline, secreted in the cortex of the adrenals was antagonistic to suprarenalin and para-sympatheticotonic (or vagotonic), that idothyrin is sympathicotonic, etc.... it is, therefore, impossible to separate the study of the function of the endocrines with the function of the nervous system of vegetative life.

To study the pathological functional endocrine syndromes, without simultaneously studying the disturbances of the sympathetic and, more generally, the nervous system of vegetative life would be arbitrary and incomplete. For this reason, the study of the sympathetic has been included in this volume. The chapters by Dr. Guillaume give an excellent anatomical introduction and the descriptions of Dr. Harvier give it a splendid starting point which will be of great help to the reader.

II. THE CLINICAL ENDOCRINE SYNDROMES.

In spite of the frequency of endocrine disturbances, very often their existence and significance is misunderstood. As time goes on, new methods spring up to help us locate and identify them. In these introductory pages, it is not amiss, after having shown the complexity of altered endocrine functions, to show the influence exerted by the sympathetic and to recall the facts which the clinician must base himself on, in order to reach a diagnosis and treat the case.

We must keep in mind the various types of lesions which give rise to endocrine symptoms. Next to the cases with mild lesions, we have others which are quite severe. The clinical interpretation and therapeutic application of the facts must be very different.

In certain cases there is a congenital lesion; for instance, when there is agenesis of the thyroid, resulting in myxedema or cretinism. More often we have to deal with acquired lesions: neoplasm or inflammations. The neoplastic lesions may vary considerably; they may be benign without any other importance than their location, such as, the colloid goitres, certain adenomata of the pituitary or of the adrenals. They may be epithelial or sarcomatous lesions, as have been reported in the thyroid, the adrenals or the pituitary; to the symptoms associated with destruction of the gland, may then be associated those resulting from hypertrophy of the affected organ. Furthermore, the malignant tumor may show signs of cachexia due to the secretions (certain cancers of the thyroid).

The histological study of a great number of benign or severe tumors has shown the part played by the hyperplasia of the organ, more often dyshyperplasia than true hyperplasia and the resulting abnormal secretion, certain cases of exophthalmos, or acromegalia, for instance in which the histological characteristics undoubtedly pointed to this. Certain facts resulting from cystic tumors at the level of the pituitary show the damage which can be made by a limited lesion, sufficient to disturb the function of a gland and cause the appearance of dwarfism as in the classical case of Souques and Stephen-Chauvet.

But—and this is important in ordinary clinical work—the endocrine lesions are often simply inflammatory or specific. The study of thyroiditis, or suprarenalitis, associated with acute infections, such as, typhoid or scarlet fever has been reported quite frequently during the last few years. In the same way infectious diseases have a well-known action on the pituitary. These diseases cause, either cellular alterations, which result in acute or subacute symptoms or interstitial alterations causing chemical changes. It is mostly in tuberculous or syphilitic lesions of the endocrine glands that the symptoms appear most frequently and most characteristically. If lesions of the thyroid, the adrenals, the parathyroids, the pituitary do not respond to treatment and evolute rapidly, those due to lues, however, can be very satisfactorily treated. The physician examining a patient with symptoms of endocrine disturbance should keep in mind the possibility of neoplasms, which cannot be cured and inflammations, or irritations by compression as in the case of bony lesions of the sella turcica.

In taking the history it is well to remember the frequency of infections as an etiological factor in lesions of the endocrines. Here, as everywhere else, acquired or congenital syphilis plays an important part. Hereditary syphilis has often been found to be the cause of symptoms of endocrine disturbance. The same applies to acquired lues, be it in the case of myxedema, exophthalmic goitre, infantilism or Addison's disease. Frequently, it appears to be the essential cause of the appearance of the symptoms. In certain cases the lesions produced are destructive, but in a great many, antisyphilitic treatment, combined with organo therapy, can cause remarkable changes, notably in syphilitic thyroiditis. In other cases tuberculosis is responsible for the symptoms and will cause the appearance of pluriglandular syndromes.

Syphilis explains very often the influence of heredity, but there is also an endocrine heredity. This heredity has been noticed particularly in thyroid pathology; it can be direct. Families of myxedematous individuals have been reported (Brissaud), hereditary or family exophthalmic goitre has been studied. It can be more complex; a mother having Basedow's disease can have children with myxedema. Similar findings have been made in regard to the pituitary, the adrenals, the pancreas, etc. It is possible that the well known heredity of disturbances of nutrition. or obesity are due to hereditary endocrine disturbances. The study of patients with endocrine disturbances should, therefore, not only include the investigation of the family for any evidence of lues, but other infectious diseases which manifest themselves in the children as disturbances of the endocrines. Emotions may possibly play a part in the etiology of endocrine disturbances. This has been known for a long time in the case of exophthalmic goitre and the late war has verified the influence of severe emotions and fright on this disease. We know the action of emotions on menstruation (periods delayed or ahead of time), on breast feeding, certain disturbances related to the internal secretions of the ovary (frequency of Chlorosis at Nancy-French Lorraine, during the years the town was bombarded, Etienne and Richard).

A large series of experiments, notably those of Cannon and his co-workers, have shown the existence of a hypersecretion of suprarenalin as a result of emotions. Changes in the adrenal secretion are liable to secondarily affect the secretion of the thyroid; these experiments have also shown a decrease in the secretion of suprarenalin by the inhibition of the gland in certain severe emotions. These facts, when related to clinical observations, allow us to agree with Laignel-Lavastine that emotions are liable to be the starting point of endocrine disturbances. What we know of the sympathetic and the part that it plays in the function of the vascular glands helps us further to understand this possible action. But as in all other cases in which emotions are blamed as a possible cause, the exact part played by them remains complex and hypothetical. It is often exaggerated and it is necessary in each case to determine exactly the importance of the emotional element.

THE EXAMINATION of patients suffering from Endocrine disturbances is taken up in the various chapters of this volume. Sometimes our attention is drawn by the alteration of the gland itself. The hypertrophy of the thyroid in certain cases of goitre makes us look for alterations of the gland. The absence of the testicle or their atrophy after mumps makes us look for bony changes or other signs associated with testicular insufficiency. The evidence of a cerebral tumor, associated with bitemporal symptomatic hemianopsia due to retro-chiasmic irritation, makes us think of a lesion of the pituitary causing the various symptoms associated with lesions of this gland. There are, therefore, two types of symptoms: signs of a tumor, or anatomical alterations of the endocrine glands, or of the surrounding tissues, causing secondarily symptoms of compression, or irritation and functional signs, showing the aberration of the secretions with exaggeration or decrease of the secretions. The first are usually easy to see, but may be absent when the second are present; these alone are sufficient to often suggest therapeutic intervention. The study of the thyroid shows numerous examples of this.

The functional signs should always be looked for, whether the signs of glandular anatomical disturbance are present or not. They seem to have a predilection for certain systems. For instance, disturbances in growth, such as, dwarfism, gigantism, etc., are usually due to disturbances of the sexual glands, the thyroid, the thymus, the pituitary. What I have previously said of the morphogenic function of the endocrines, of their harmozones which regulate development, shows the primordial importance of disturbances of growth. It was believed, for a long time, that the thyroid alone was responsible for infantilism. We now know the part played by the pituitary, the thymus and possibly the pancreas. The part played by the pituitary and the thyroid on the genital glands and growth is well known. All disturbances of growth should suggest to the physician an investigation of the function of the endocrines.

Outside of disturbances of growth, alterations of the bony tissues are often of endocrine origin. Acromegalia is an example of this, so is rickets, osteomalacia, and many other bony affections have been found to be of endocrine origin. Recently, Professor Hutinel has shown how the study of any dystrophy of the bones should suggest an investigation of the endocrine system. Articular alterations are sometimes related to a certain degree to endocrine lesions; chronic rheumatism is often associated with thyroid insufficiency (Lancereaux, Paulesco, Souques and Sergent) and clinical investigations in some cases reveal the influence of the testicle, the ovary, the pituitary and other glands. Here again, we should not limit ourselves to the study of the endocrines and the possibility of acquired or congenital lues should be investigated.

Disturbances of the genital organs, male or female, be they primary or secondary to a known endocrine lesion, should always lead to investigation of the possibility of the disturbance of some other endocrine gland.

Precocious amenorrhea has often revealed an alteration of the thyroid or the pituitary. Impotence in the male, while it is often the result of some acquired testicular lesion is sometimes the sign of late infantilism of pituitary or thyroid origin. In the same way, the absence of development of the genitals in a young man is sometimes due to the thyroid or pituitary causes of infantilism. Inversely, hypersecretion of the ovary or hyperorchitis suggest adrenal or pituitary lesions and Harvier has brought together the well-known facts of suprarenal virilism, hirsutism or pituitary obesity with precocious development of the genital system.

The various manifestations at the level of the skin or its derivatives is very important. Squamous skin, ichtyosis, wrinkled or senile skin, are symptoms of thyroid insufficiency. Dryness of the skin, decreased or absent secretions have also been reported when there was a thyroid insufficiency. Attacks of sweating have inversely been noted in cases of hyperthyroidism. Pruritus, urticaria, circumscribed edema, certain eczemas are also manifestations of endocrine disturbances. Disturbances in the cutaneous pigmentation, and specially melanodermia are of great value as indicating some change in the adrenals. The loss of hairs, particularly the partial loss of the eyebrows has been given as an evidence of abortive myxedema (Leopold-Levi and Rothchild). This is also observed in certain affections of the pituitary. Inversely, we see an exaggeration of the development of hairs in certain cases of suprarenal virilism or hirsutism. Teeth easily affected, or absent, belong to this same group of symptoms and in children the persistence of the milk teeth and the superposition of the two dentitions is sometimes a sign of hypothyroidism as I have observed with Mrs. Long-Landry. The nails can be also altered striated, with many white marks, thin and easily breakable. The examination of the hairs, the nails, the teeth, added to that of the skin, is essential whenever an endocrine lesion is suspected, particularly a thyroid disturbance.

Among the disturbances in nutrition which go hand in hand with changes of the skin and its derivatives, *obesity*, holds an important place as being one of the most frequent signs of endocrine disturbance. Be it associated or not with bone, genital or skin lesions, it has often been caused by an insufficiency of the thyroid. There are also more complex causes; that is, it may be due indirectly to an action on the genital glands by the thyroid. Next to the thyroid in frequency and possibly more often, the pituitary is involved. Occasionally the pineal and the adrenal glands are to blame. Certain syndromes, such as, Dercum's disease appear distinctly as polyglandular syndromes, in which at least three glands are involved: ovary, thyroid and pituitary, and possibly, also the adrenals. In all cases an endocrine disturbance should be suspected in cases of obesity, particularly if it shows evidence of partial obesity, be it painful or not. Obesity associated with thin limbs is very characteristic in certain adiposo genital syndromes of pituitary origin.

Next to obesity, we must place diabetes mellitus, which often leads the way to the discovery of an endocrine disturbance. Next to pancreatic diabetes, clinically and experimentally, so clearly specific, there are diabetes due to thyroid disturbances. Glycosuria has frequently been noted during exophthalmic goitre. Other cases seem to bear some relation to disturbances of the pituitary, the occurrence of diabetes during acromegalia is not exceptional; if at first the origin might be pressure on the floor of the third ventricle (Loed, Launois, Roy, Marcel Labbe), instead of a functional pituitary deviation, it is nevertheless, occasionally a suggestive sign in divulging a pituitary lesion. Finally, adrenal diabetes has attracted considerable attention and we recognize more and more the importance of this gland in the etiology of certain cases of glycosuria. The investigation of a possibility of glycosuria, the appreciation of its degree and rythm can put us on the track of an endocrine disturbance. The relation of glycosuria to the injection of suprarenalin or pituitrin has suggested certain very interesting conclusions which in the future may be of considerable clinical importance.

Diabetes insipidus, more so than diabetes mellitus, can have a clearly defined significance, and a series of recent studies has shown its value as an indicator of para or pituitary disease; the injection of the extract of the posterior lobe of the pituitary will temporarily cause the polyuria to disappear in certain cases. Investigations should, however, be carried out on the possible influence of the nervous system, which has been brought out by the recent work of Camus and Rousey who were able to cause a polyuria by irritation of the floor of the 3rd ventricle.

Intellectual and mental disorders should also be investigated. We have known for a long time that backwardness, imbecility, idiocy, etc., have been recognized as being the result of myxedematous hypothyroidism. This is also recognized as the cause of torpidity and sleepiness, mental instability and various psychoses occur quite often in Basedow's disease. In the same manner, in acromegalia many cases have been reported suffering from melancholia, desire to commit suicide and, particularly, torpidity and mental confusion. Patients with Addison's disease are sluggish; those with Dercum's disease melancholic. Grouping together all these facts Laignel-Lavastine a few years ago was able to bring together the psychic disturbances and abnormality of the endocrines. These disturbances are, however, not sufficiently systematized to be as valuable indicators as changes in the skin, nutrition, etc. All that can be said at present is that in view of our ignorance of the cause of the development of certain intellectual changes, the investigation of disturbances of the endocrine may be of value. This is the case in the mental changes during puberty and the menopause and perhaps such an investigation may result in interesting therapeutic conclusions. Nervous symptoms; such as, epilepsy or tetany, are in certain cases indicative of endocrine disturbances. Generalized tetany, as seen in infants, in pregnant women, and in adults, is probably an indication of parathyroid deficiency, whether there is a deficiency of calcium or not.

Another illustration of symptoms of endocrine origin can be found in cardio vascular symptoms. We have known for some time that hypotension and certain associated manifestations, such as, the white line of Sergent, have been considered as due to adrenal insufficiency. The prognosis of certain acute affections (scarlet fever, typhoid, etc.) has often seemed to depend on whether or not the adrenals were affected, so much so, that a real adrenal syndrome has been found in acute infections having as a starting point cardio vascular changes. Inversely, arterial hypertension seems in certain cases to be due to an increase in the adrenal secretion. Dr. Harvier has studied these various syndromes in this volume. We must, always be very careful in their interpretation, but it is certain that the investigation of the causes of disturbances in arterial pressure may be of value in endocrinology.

It is not my intention to describe in this introduction all the symptoms and syndromes related to the pathology of the endocrines. Each day the list grows longer. Each organ of the body can furnish an example of it. Above everything else it is the disturbances affecting the morphology of the individual, by altering his nutritive metabolism, which have a diagnostic value, and it is, therefore, on these that we must insist. It goes without saying that a complete examination may reveal may others. Such an examination will bring out the whole syndrome of thyroid insufficiency or hyperfunction. It will make the diagnosis of pituitary or adrenal lesions. Each gland has its own symptomatology and Dr. Harvier has very correctly insisted on these various suggestive syndromes. All do not have the same accuracy. For instance, the symptomatology of the thyroid is now very definite, thanks to the publications of Leopold-Levi and Rothchild, and is particularly easy to understand, due to the results of thyroid organo therapy. Pituitary symptomatology is beginning to be better known, but adrenal symptomatology has not yet been definitely defined. The respective parts played by the glandular and by the sympathetic nervous system disturbances are hard to judge even in cases of Addison's disease. Arterial hypotension which invariably results in adrenal insufficiency can be due to so many different causes that alone it cannot be considered as indicative of adrenal insufficiency.

For this reason, it would be very important during acute or chronic diseases to have definite signs of the functional capacity of the various endocrine glands, to be able to have endocrine tests similar to those performed in pathological conditions of the kidney and liver. In the same way, it would be very useful to have various signs to enable us to define the intervention of the sympathetic nervous system in the symptomatology under observation.

At the present time our observations are still very indefinite. It is only fair to say, however, that the injection of suprarenalin and of pituitrin (posterior lobe) has been tried lately and has often given very interesting results. Not only has the subcutaneous injection of suprarenalin cardio vascular effects, which have been known for many years, but it can, with or without the injection of sugar give a glycosuria more or less marked (Blum) accompanied by a hyperglycemia, the significance of which has been very much in dispute. Somewhat similar to this suprarenalin glycosuria is pituitary glycosuria which was discovered by H. Claude and A. Baudouin. They consider that glycosuria is a normal consequence of an intramuscular injection of the posterior lobe of the pituitary, previously purified and the lipoids having been removed, provided it is followed by a meal containing sugar (preferably one half hour afterwards); this glycosuria is noticed particularly in patients suffering from arthritis, is absent in tuberculous individuals and is more abundant than suprarenal glycosuria under similar conditions. To this glycosuria are added cardio vascular phenomena studied by H. Claude, R. Porak and Routier and consist in more or less marked changes in the tension of the pulse. H. Claude, together with R. Porak, has recently tried to make biological tests of these re-actions of suprarenalin and pituitrin so as to be able to bring out lesions of these glands in mixed glandular syndromes. For instance, the glycosuria and cardio vascular re-actions, following the injection of pituitrin are absent in acromegalia. In patients with Basedow's disease, the cardio vascular re-actions are exaggerated after the injection of suprarenalin or pituitrin. In thyroid insufficiency the glycosuria and the drop in systolic pressure are normal, but the acceleration of the pulse occurs instead of slowing. In patients with Addison's disease there will be no glycosuria and the systolic pressure will rise instead of going down.

Without doubt it is too early to deduct from these tests, definite conclusions. They are liable to occur in transitory endocrine disturbances after infectious diseases, for instance, without this being an indication of any permanent lesion of the gland. Nevertheless, they are liable to give us some idea of the endocrine equilibrium and when we understand these reactions better we probably will be able to refer to them clinically to help us in diagnosis.

These tests, furthermore, bring out the intervention of the sympathetic. It is the stimulation of this system which after the injection of pituitrin inhibits the fixation of glucose by the liver, its stimulation seems to play a part in certain of the effects of suprarenalin. Lately, the injection of suprarenalin has been used as a method of showing up excitability of the sympathetic. Dr. Harvier has gone over in detail the various plans of this subject, particularly those of Eppinger and Hess on the injection of suprarenalin on one side and atropin and pilocarpin on the other. The injection of suprarenalin is inactive in some, in others it causes an increase in the blood pressure; tachycardia, polyuria, glycosuria with or without the previous injection of glucose, dilatation of the pupil, etc. It stimulates the sympathetic and such individuals are called sympathicotonic. Pilocarpin inversely, in predisposed individuals, causes a marked tachycardia, sweating, salivation, nausea, vomiting, spasms of the intestines, colic and diarrhea. In others, it is without effect. It stimulates the vagus nerve in the first type of case, which is called vagotonic. In the same manner atropin paralyzes the vagus and in sympathicotonic individuals will cause a tachycardia, dilatation of the pupils, dryness of the mouth, etc. This division of patients into vagotonic and sympathicotonic has been further investigated during the last few years. The oculo cardiac reflex is a great aid in this respect. When positive, that is, when there is slowing of the pulse after ocular pressure, it indicates vagotonia; negative, that is, when there is an acceleration of the pulse is considered to be a sign of sympathicotonia. In spite of a certain reservation which we must make for this test it is, nevertheless, a very useful sign whenever we are investigating the sympathetic system.

The study of the sympathetic is extremely fruitful and complex and recent investigations indicate how much our knowledge is increasing every day. It is, however, difficult to determine its limits. The nervous system of vegetative life can be affected in many ways, often by the intermediary of a gland of internal secretion. Actually, as Dr. Guillaume has described, it consists of the true sympathetic and the cranial and pelvic parasympathetic system. It is in the cranial parasympathetic that we must include the vegetative fibres annexed to the vagus which exert their action on the respiratory system, the gastro intestinal tract and its adnexa and the heart. It is by the intermediary of these fibres that the association reflex, such as, the oculo cardiac reflex occur. It is also the case in these reflexes showing the connection between the nuclei of the vagus and the general sensory tracts or those showing the functional sympatehico-parasympathetic mechanism. These examples show how many symptoms can result from disturbances of the normal mechanism of the sympathetico-parasympathetic apparatus. In the cases in which the equilibrium between these two systems is normal there are some (among which are the vagotonics we have previously referred to) which show a hypertonia of the parasympathetic which is discussed by Dr. Harvier in this volume. They have a slow pulse, myosis, sunken eyes, are pale, have abundant and easy perspiration, hypersecretion of saliva, bronchial and intestinal secretions. Pilocarpin exaggerates these symptoms. The oculo cardiac reflex indicates a hypertonia of the vegetative vagus system and numerous other symptoms also indicate this. Others have hypertonia of the sympathetic which manifests itself by protrusion of the eyeballs, mydriasis, warm skin, tachycardia, decrease in secretions, slowing down of digestion, contraction of the sphinxters resulting in constipation. Secondarily, the suprarenal and thyroid secretions are increased and cause various phenomena. These individuals react to certain pharmacological substances, notably suprarenalin, which sometimes brings out certain confuse symptoms.

These two syndromes are, however, not always dissociated clinically. We can have a resulting syndrome of hyperactivity of the two systems, with neutralization in antagonistic territories corresponding to what Hess and Eppinger have described under the name of vagotonia. It is better defined, as suggested by Dr. Guillaume, under the name of neurotonia (meaning hyperneurotonia). This neurotonia syndrome groups together a number of sick people, nervous system invalids, which complain of gastric disorders, cardiac disturbances, and various symptoms of neurasthenia. The investigation of the various reflex reactions is a great help to prove the existence of this syndrome. The oculo cardiac reflex is positive; atropin, pilocarpin and suprarenalin cause suggestive symptoms in these subjects. To understand this syndrome all that is necessary is to notice the symptoms which accompany emotions; the emotional neuro vegetative phenomena being neurotonic. The patients, which Dupré had in mind when he studied the emotional constitution, certainly were neurotonic. In the gastric neurosis we also find many examples of neurotonic individuals; that is, disturbances due to modification of the two nervous systems of vegetative life.

We see without insisting further, the multiple clinical manifestations which may result from disturbances of the nervous system of vegetative life. These also result in reactions far away; reflex, neuralgia, tonic disturbances, symptomatic visceral affections and many others.

In spite of the many new discoveries relating to the pathology of the sympathetic, its symptomatology is still extremely obscure. The conception of neurotonia and of the balance which normally exists between the sympathetic and parasympathetic system certainly helps us in analyzing clinical facts. These can still better be interpreted, thanks to the various reactions we have mentioned (oculo cardiac reflex, atropin, pilocarpin or suprarenalin tests). It is to be hoped that in the near future the physio pathology of the sympathetic system and its symptomatology will be possible to study from a practical point of view.

At the present time, we limit ourselves to the observation of the effect of certain endocrine disturbances on the function of the sympathetic and parasympathetic and the no less definite action of these systems on the endocrine glands. We must, however, remember that there are direct connections between the endocrine glands without the intervention of the nervous system, so that functional alterations of a gland may occur without the intervention of one of these systems.[1]

From what I have just said we see that the clinical study of the patient allows us, by the investigation of a series of symptoms, to look out for the possibility of some endocrine alteration, to sometimes fix the chronology of the various accidents and to reach certain therapeutic conclusions. Very happily, the treatment of patients has very largely benefited by these progresses in clinical investigation. The conception of the part played by the sympathetic and the parasympathetic, is very important and there is no question but that many therapeutic effects are exerted by the intermediary of this nervous system. It is, therefore, to be hoped that the progress in endocrinology and the study of the sympathetic, will enable us to better understand the neuro glandular disturbances allowing us to appreciate better the therapeutic indications and the most efficacious method by which these can be employed.

III. GENERAL THERAPY OF DISEASE OF THE ENDOCRINES.

In the preceding chapters I have brought out the well-established action of certain glands in the etiology of certain definite diseases: the thyroid in myxedema and exophthalmic goitre, the pituitary in acromegalia, the adrenals in Addison's disease. I have also shown, next to these fairly simple examples, others more complex, in which the action of the endocrine glands was exerted on other glands. Such is the case of infantilism which may result from the effects of the thyroid, or the pituitary on the genital organs. There are other cases in which several endocrine glands are simultaneously affected, bringing on pluri-glandular syndromes, the clinical explanation of which varies: obesity of the menopause, Dercum's disease, sclerodermia, certain types of senilism or of genito-dystrophic gerodermia, are examples of these types of cases. Whether we are dealing with such cases or others apparently simpler, we must not forget the part played by the sympathetic nervous system, which is very evident in certain diseases (Addison's), but more obscure in others.

---

[1] It is well to remember that the part played by the nervous system is much more extensive than is at present admitted in the production of symptoms which are believed to be of endocrine origin. Recent experimental researches as well as anatomical and clinical observations seem to show that the symptoms, believed to be due to pituitary lesions (polyuria, adiposes, infantilism) can be produced by purely nervous lesions of the floor of the third ventricle (Camus and Roussy). A case of so-called pituitary infantilism, on which an autopsy was performed in front of the writer and Dr. Cathala and Mouzon, showed a normal pituitary,while there was a tumor of the third ventricle. It is therefore possible that endocrinology, while correct as a whole, may have to be revised as to its details.

Clinical investigation allows us to bring out certain alterations of the endocrine glands, but what is often not brought out is the nature of the functional glandular disturbance, which causes the symptomatology: insufficiency, aberration, hyperfunction. I have already said how difficult it was to decide and how very careful we must be of our interpretations, always, however, remembering the importance of aberrations by insufficiency which are particularly efficaciously treated therapeutically.

Finally, we must remember that in endocrine pathology, outside of new growths a large place must be kept for inflammation, and that rheumatism, tuberculosis and syphilis are often the cause.

The pathology of the thyroid, of the pituitary and of the pancreas shows numerous examples of this. The possibility of a luetic infection must be remembered and may be very useful when the question of treatment comes up.

Our therapeutics can be etiological and aim at treating the disease which has caused the inflammation of the endocrine glands. It can by radiology, or by surgical intervention attempt to act directly on the diseased gland. It can finally attempt to supplement or stimulate deficient functions, and more rarely inhibit them.

I. ETIOLOGICAL TREATMENT.

However logical this method may appear, it is only rarely indicated. Naturally, when lues is the etiological factor, antisyphilitic treatment should be attempted; while recommended in thyroid and pituitary affections it has, however, only a limited effect, limited by reason of the lesions which must be remedied. When destructible, it cannot, even when healed, bring back the regeneration of the organ; gumma of the thyroid, of the pituitary leave sclerous lesions, which are incompatible with a normal function of the gland. The treatment, moreover, cannot change certain lesions in the neighborhood, such as, alteration of the chiasma of the optic nerves which is so often noticed following affections of the pituitary. In spite of its limited effect, antiluetic treatment should always be attempted whenever a syphilitic origin is suspected, associated with organo therapy it seems to definitely help in improving the condition in many cases; its action has been noticed in certain cases of myxedema due to a thyroiditis of specific origin. It seems to act in the same way in certain syndromes of pituitary origin, if not on the pituitary lesion at least on the meningitis, which is often associated with it. In other cases anti-rheumatic treatment will be beneficial. Sodium salicylate has been specially recommended in exophthalmic goitre. It certainly is a great help in many cases. Since Chibret and later Babinski have advised its use; it has been administered in much larger doses and not simply as an antirheumatic agent. In the same manner quinine plays a part in endocrine therapy and we cannot say that its use should be limited only to cases of malaria. Tuberculosis sometimes causes endocrine manifestations and this fact may be of value in certain therapeutic indications.

In spite of all this, etiology does not help us very much in the treatment of these patients and the knowledge that we are dealing with functional disturbances by deficiency or excess, which we must attempt to modify, has done much to bring about a marked improvement in the condition of our patients.

II. SURGICAL TREATMENT.

Surgical interference is rarely indicated in endocrine pathology. There are, however, certain definite cases in which it is of great help. We have known for many years the surgery of the thyroid. At first, limited to simple goitre and tumors, it has now extended to exophthalmic goitre and if intervention is still often questionable, because of the danger, it can be considered as rational in certain cases, as for instance, those recently studied by Roussy. The facts established show that while there is no question of the benefit of partial thyroidectomy in Basedow's disease, it has also its drawbacks. Thymectomy has also been performed with variable success, with or without thyroidectomy. In hypertrophy of the thymus in childhood, for a while surgery of the thymus became popular as a result of the investigations of Veau, but it is now limited to very rare cases.

The surgery of the pituitary has been even more carefully studied and we are still far from having perfected it. The recent investigations in France of Lecene, Toupet and Lenormant have shown that the pituitary could be reached through the nasal route and that its removal in man was possible. The results are, however, far from what was expected after the first few cases were published. It seems as if this very dangerous intervention, which is advised in acromegalia and patients suffering from adiposo genitalis, is only indicated when, to the symptoms of pituitary disturbance, are added serious evidences of hypertension (headache, alteration of vision), and when the X-ray also shows a marked enlargement of the sella tursica. The removal of the pituitary is never complete; it is necessarily a partial operation and is purely palliative. It seems as if in certain cases all that is done is to decompress the affected region. The recently published observations of Lecene and Morax verify this hypothesis, as by causing a falling down of the deep wall of the sphenoidal sinus, that is, the floor of the sella tursica, without touching the pituitary, Lecene was able to cause the disappearance of an adiposo genitalis syndrome, associated with marked signs of hypertension, notably ocular disturbances with changes in the disks, which were also improved by the operation. A simple decompression has occasionally given similar results. Pituitary surgery, therefore, is still a method only to be used exceptionally, and aims more to relieve hypertension than the pituitary lesion. However, the results of decompression of the sella tursica, as performed by Cushing and Lecene, show that this method might be used in certain cases.

However limited at present is the surgery of the endocrines, it is indicated in removable tumors, (certain thyroid tumors for instance) or to modify the consequences of certain neoplasms which, as in the case of the pituitary, cause secondary symptoms by direct pressure or by hypertension. It cannot be said, however, that endocrine surgery is a method we can hope very much from in the future, since it can only act in tumors and their consequences. It cannot remedy a glandular deficiency, the usual result of an endocrine lesion.

Its usefulness in certain disorders of sympathetic origin is also limited. However interesting might be the interventions attempted in the past by Jaboulay and Jennesco, of resection of the cervical sympathetic in exophthalmic goitre, less severe methods will probably give better results.

III. TREATMENT WITH X-RAY.

The glandular cells are susceptible to the X-rays and these can decrease their function. This is, however not, without certain drawbacks and a classical case has shown the etiological influence of radiotherapy, directed against hypertrichosis, in producing manifestations of myxedema, previously modified by thyroidien organo therapy (Acchiote). This is not an isolated case, and such facts suggested that these rays might be usefully employed in cases in which hyperfunction of certain glands was suspected.

X-ray has been used for many years in the treatment of fibroma and it was believed that its action on the ovary by causing premature menopause, would modify this condition. This theory has been found to be incorrect, for we know now that radiotherapy has a direct action on the fibromatous tissue. It is, nevertheless, true that X-ray causes a decrease, then a cessation of the periods and anatomically brings about a degeneration of the Graafian follicles, while in man it will stop the evolution of the spermatozoa.

The atrophic action of the X-rays has been tried on the thyroid, in cases of exophthalmic goitre and very variable results have been obtained. In 1911 P. Marie, Clunet and Raulot-Lapointe by using large doses of very hard rays, obtained remarkable results, as regards the constancy and regularity of the evolution of the phenomena observed. However, not all cases are improved and radiodermia, which is particularly liable to occur on the neck, is often an obstacle to the use of this type of treatment. For this reason, this procedure is not the method of choice; furthermore, hyperfunction is not the only cause of Basedow's disease and the theory of dysthyroidism possibly explains some of the failures of the method.

The pituitary seemed to be susceptible to the X-rays and Beclere has advocated its use in certain cases of acromegalia. The few cases in which improvement was observed allow us to believe that it may be possible to stop the early evolution of acromegalia and gigantism by radiation, and that it might also be possible to modify some of the symptoms of adiposo genitalis with ocular symptoms. Unfortunately in such cases, there is such a mixture of symptoms of insufficiency and hyperfunction that we cannot expect much from radio therapy; which is, moreover, difficult to apply and if Beclere, Jaugeas and others have reported favorable results, here again, as in exophthalmic goitre, we must abstain from any premature conclusions.

Zimmern and Cottenot have thought that the adrenals could be affected in a similar manner. They believed that hypertension is often of adrenal origin, and that radio therapy of the suprarenal capsule through the lumbar region might be beneficial. This method, while without any effect in cases of arteriosclerotic or albuminuric hypertension, seemed to have improved real cases of uncomplicated hypertension and to have markedly reduced the arterial pressure. This method has been experimentally controlled by Zimmern and Cottenot, which has enabled them in dogs to cause destructive alteration of the medulla and of cortex of the adrenals. Here again, however, we are dealing with inconstant results which we must accept with considerable reserve.

These examples to which we must add the thymus, very easily affected by radiology according to Regaud and Cremieux, show that this method can be of value in certain cases of hypertension. This method should only be used as an adjunct to other procedures more liable to modify the glandular disturbances. It is to organo therapy that we must look in most cases as the method most liable to bring about results.

IV. ORGANO THERAPY.

This method is based on the use of the juices and extracts of tissues and has as chief aim, to remedy the absence or hypofunction of an organ, by means of extracts of similar organs taken from animals.

The extracts of organs have been utilized since antiquity, but it is only since Brown-Sequard and the first investigations of the treatment of myxedema with thyroid extract that organo therapy has become of any real value. Dr. Carrion and Dr. Hallion have covered this subject very thoroughly in this volume, so that there is no necessity to go into any detail.

Organo therapy can be accomplished in many ways. Milk and eggs can sometimes be considered as organo therapeutic products. In the same manner, certain products, such as, bile, gastric juice, are often utilized; in other cases, the active principle isolated from a gland is used. The typical example of this being suprarenalin, but it is chiefly the organs themselves, either fresh, or their extracts, obtained in various ways which constitute the majority of organo therapeutic products.

When we are using them, it is well to know what to expect of them and to be warned against certain errors in interpreting their action. Thyroid organo therapy, which is so remarkably efficacious in myxedema has allowed us to discover a triple action: substitute, homo stimulating and symptomatic.

The substitute action consists in that the extract which is administered substitutes its action for that of the deficient organ. In congenital myxedema due to agenesis of the thyroid, the extract takes the place of the absent thyroid.

The homo stimulating or auto restorative action is also easily understood; if the extract is administered when the gland is only partly destroyed it can help in the rebuilding of the organ and stimulate its function. This is so in quite a few cases of thyroid insufficiency.

To these two modes of action which can be termed specific, we can add a third which we must always keep in mind when we are watching the effect of organo therapy. An extract of an organ, like all other organic or mineral medication, has a pharmacodynamic action peculiar to it. As such it can be employed symptomatically to bring out new symptoms or suppress pathological ones; the pituitary furnishes an example of this type of action. We use pituitrin to accelerate labor or to increase intestinal peristalsis. Basing himself on the symptomatic action of these extracts, Gley has very rightly criticized the conclusions which are reached on the action of certain extracts of organs. In spite of this, symptomatic organo therapy has a big field of action and thyroid extract in small doses has shown its value in a multitude of cases.

It seems difficult, however, in the great majority of cases, not to believe in the substitute or homo stimulating effect of organo therapy. The recent investigations of J. J. Huxley on the acceleration of growth by means of very small doses of thyroid to tadpoles, his investigations on the axolotl of the salamander under the influence of the same medication show how pronounced is the action of thyroid on the phenomenon of growth. This action seems to be really a substitute one or even homo stimulating. In the same manner the very definite effect of pituitrin in diabetes insipidus cannot be considered as purely symptomatic. It only manifests itself in the case in which other signs point to a pituitary cause for the polyuria. In other cases there is absolutely no effect. It seems difficult in such cases not to believe that there is a specific action. In the same manner in suprarenal organo therapy the action is far from being purely symptomatic and predominately cardio vascular. In many cases the blood pressure is hardly affected and it is chiefly in the cases of suprarenal insufficiency that the changes are noticeable.

In all the cases of endocrine disturbances, in which some of the symptoms are clearly due to glandular hypofunction, substitute or homo stimulating organo therapy is therefore indicated. This is so in the case of thyroid medication in myxedema, suprarenalin in Addison's disease or adrenal insufficiency and ovarian medication in natural or artificial menopause.

Inversely, when hyperfunction or aberration of function with exaggeration of secretion is suspected, such type of medication would be detrimental. We know, for instance, the bad effects of thyroid medication in exophthalmic goitre. We can, however, to a certain extent rely on inhibitive organo therapy. This is the method which has led Ballet and Enriquez to use the blood of dethyroided animals on the treatment of exophthalmic goitre, or which we employ when we give pituitary extract in the same disease. As the physiological action of the various endocrine glands is better known and their interglandular relation is better understood, such type of organo therapy will be used more frequently, and will become more definite. Already the theory of glandular hormones has enabled us to understand how certain types of organo therapy exert a stimulating action on other glands than the ones injected. If the conception of *Chalones* suggested by Schæfer is ever proved; if it is ever established that certain endocrine glands, have under certain conditions an inhibitive effect on other glands, then the therapy of glandular hyperfunction or dyshyperfunction will have made a great step forward. This chapter is, however, only at its beginning.

There are cases, becoming more and more numerous, in which, organo therapy must be complex. I have already insisted too much on the importance of polyglandular syndromes and the frequency of a simultaneous alteration of several glands, to say more on this subject. We must oppose an associated organo therapy to multiple functional disturbances. In some cases, it is best to give each one for a certain period, in other cases the extracts of various glands should be given simultaneously. I find more and more, that I have to use preparations containing a combination of: thyroid, pituitary, ovarian and adrenal in varying proportions. When administered in syndromes, such as, Dercum's disease, glandular obesity, sclerodermia, certain cases of infantilism, etc., these organo therapeutical preparations seem to act very favorably. It even seems as if thyroid medication was better tolerated when combined with either adrenal or pituitary extract. When medication has to be carried out for a long period of time the association of these extracts is particularly indicated.

We must finally remember that the good or bad results of organo therapy can occasionally help us in diagnosis; this has been established by Gilbert and Carnot. It is by means of this method that Leopold Levi and H. de Rothschild have shown the numerous consequences of a mild thyroid insufficiency. It is, also, by this method that the

LANE LIBRARY

part played by the liver and pancreas in the production of diabetes has been established by Gilbert. No doubt we must, as suggested by Gley, Camus and Rousey, make certain reservations on the significance of the results of therapeutic investigations by these extracts. It would however, be unfair not to believe that they have at least some value.

Simple or complex organo therapy has lately given remarkable results, and each day we see new indications arising. It, however, necessitates a definite technique and careful watching. The many accidents resulting from excessive or irrational thyroid medication is well known; in the same manner suprarenal medication is not without its drawbacks. The various methods of administering these extracts either by mouth or subcutaneously, deserve a certain amount of study, but Dr. Carrion has covered this subject very carefully so that it is not necessary to go into details. All that I will say, is that at the present time, dried extracts are far superior to fresh ones, except in certain exceptional cases. We must remember that the preparation of these products is very delicate and for this reason only reliable products should be employed.

The mode of administration, according to the extract employed, has a considerable importance. Oral administration is the simplest method, and in prescribing thyroid or ovarian extract, no other way need be used. The constant results obtained by this method of administration has been proved in many cases. The report of Murray on a case of myxedema who was kept in good health for 28 years by the ingestion of thyroid extract by mouth shows this well. It is, however, evident that other products are less active when administered in this manner; certain gastro intestinal juices seem to affect them, for instance, pancreatic extracts are affected by the gastric juice.

Attempts have been made to get around this by surrounding the extracts with gluten, wax or keratine, without however obtaining constant results. Rectal administration has been advocated and it seems as if macerations of fresh organs (liver or pancreas) have a real activity. This method, however, cannot be used for constant medication. It is administered at bed time and laudanum is added to it so as to prevent its expulsion.

Subcutaneous injection was for a long time believed to be impossible, because of the drawbacks resulting from the administration of albuminoid materials under the skin. We now know that we can administer under the skin, without any inconvenience, certain preparations, from which the lipoids have been removed and which have been sterilized. The thermostable substances which they contain, still retain a certain number of characteristics. If such a method is without value in the case of the thyroid, it is very useful in the administration of pituitrin or suprarenalin. In certain severe anemias, the extract of bone marrow seems to act very quickly and very definitely. It is, therefore, not always advisable to abstain from administering endocrine products subcutaneously. The only method which should be avoided is the intravenous route which sometimes will cause severe accidents. In spite of this, it has occasionally been recommended to administer intravenously the posterior lobe of the pituitary is hemoptysis. I believe that it is safer not to do so.

Organo therapy when properly administered has given remarkable results, providing it has been given regularly and over a long enough period. Too often the diagnosis of an endocrine lesion is associated with that of some organic lesion which cannot be cured or modified very much. Organo therapy, which is the treatment of functional disturbances, can ameliorate the symptoms. It can even modify them by changing the functional disturbances. Thyroid medication has shown this clearly. Perhaps less striking are the results of adrenal medications in diseases of the adrenal glands. Pituitary medication has also given excellent results. The action of mixed organo therapy has proved itself in many cases of polyglandular syndromes and the fact that the medication must be kept up is not an argument against the value of this type of treatment. It certainly is a fact that by this type of medication results are obtained which otherwise would be impossible. Unfortunately, the dose to use and the procedure to follow varies in every case. Due to the lack of familiarity with the pathology of this subject, many physicians neglect cases which could be benefited by this mode of treatment. By explaining the pathology and showing the various therapeutic indications of endocrinology, Dr. Harvier has enabled the physician to detect the various types of cases which might be helped by this form of treatment.

THE PATHOLOGY OF THE ENDOCRINE GLANDS

BY DR. P. HARVIER

Physician to the Paris Hospitals.

PATHOLOGY OF THE THYROID.

FUNCTION OF THE THYROID.

The thyroid is a gland surrounded by a fibrous capsule from which partitions arise which divide it in lobes. Each one of these lobes contains a series of closed vesicles, of various sizes, and without any excretory canal.

The walls of the vesicles are lined with epithelium, made up of two types of cells: the main cells, which have a round nucleus with a clear protoplasm and colloidal cells, which are polymorphous, have an oval nucleus and a protoplasm filled with acidophil or basophil granulations.

The cavity of the vesicle, oval, or spherical, contains a thick secretion, more or less yellow, which has been termed colloidal substance.

The secretion of the thyroid is made up of several products, the most important of which contains iodine. Chemists have extracted it from the colloid and Baumann has designated it under the name of Iodothyrin. We know to-day that Iodothyrin is only one of the components of the thyroid secretion and that it is furthermore an artificial product, not well defined, and made up of several compounds. According to Oswald, the colloid contains at least two substances: 1—A globulin or thyroglobulin which contains all the iodine of the gland as an organic compound and from which iodothyrin is derived; 2—A nucleo protein, which does not contain any iodine, but instead other minerals, phosphorus and arsenic in particular.

Iodine when introduced into the organism is fixed by the thyroid. The quantity varies in each species and in each individual according to the food. It cannot be considered as an index of the activity of the thyroid.

The functions of the thyroid have been elucidated by the observation of the various phenomena following the extirpation of the thyroid and by the physiological effect of the thyroid extract and finally, by the results obtained by giving experimentally excessive doses of thyroid.

I. PHENOMENA FOLLOWING THE REMOVAL OF THE THYROID.

In animals thyroidectomy produces two types of phenomena:

1.—ACUTE SYMPTOMS which consist of post operative tetany and are due to the simultaneous extirpation of the parathyroid glands.

2.—CHRONIC SYMPTOMS are the only ones which are really due to thyroid insufficiency. They are particularly marked in the young during the stage of growth. The dethyroided animals are small and deformed, as compared to the controls. Their skin is infiltrated with an indurated edema; at the same time it becomes dry, wrinkled squamous, the hairs lose their brilliancy, and fall out. The growth of bone is stopped and the genital organs (testicle or ovary) become atrophic. These animals become sad, slow, apathetic and appear idiotic.

These accidents occur the more rapidly if the animal is young.

The thyroid gland, therefore, secretes a substance necessary to the organism; the absence causes the appearance of trophic symptoms. If in a dethyroided animal a graft of thyroid gland is made or it is given the extract of thyroid, these accidents are avoided.

II. PHYSIOLOGICAL ACTION OF THYROID EXTRACT.

Thyroid extract has a very definite effect on the blood pressure, the cardiac rhythm and nutrition. Schaefer in

1895 showed that the intra venous injection of thyroid extract caused a drop in the blood pressure. Heinatz noticed the marked acceleration of the heart and pulse following its injection.

All the observations concerning the action of thyroid extract agree that there is a loss of weight following the injection of thyroid, even when the food is abundant and at the same time, there is an increase in diuresis, and of elimination of urea and nitrogen.

III. EXPERIMENTAL HYPERTHYROIDISM.

Ballet and Enriquez by having animals absorb large doses of thyroid were able to observe a syndrome of hyperthyroidism characterized by tachycardia, fever, nervous disturbances (restlessness and tremor), followed by loss of weight and diarrhea.

All these physiological and experimental facts allow us to interpret the various syndromes of hypersecretion, and insufficiency observed in man.

CHAPTER I.

I. THYROID INSUFFICIENCY SYNDROMES.

An insufficiency in thyroid secretion results in a series of dystrophic conditions known under the name of myxedema.

1. ADULT MYXEDEMA.

This condition was described by Gull (of London) in 1873 under the name of cretinism. It was studied by Ord who suggested the name of myxedema, then investigated in France by Morvan and by Charcot.

It occurs between the ages of 30 and 60, more frequently in women than men, usually as a result, sometimes a long time afterwards, of some *infectious disease*; articular rheumatism, typhoid, scarlet fever, etc., which has affected the thyroid and altered its secretion.

The condition begins very insidiously and is at first marked by fatigue, weakness, persistent anemia and a gradual intellectual stupor. It is finally characterized by three important symptoms: *infiltration of the tissues, atrophy of the thyroid and mental degeneration.*

1.—INFILTRATION OF THE TISSUES.—The appearance of the patient is typical. "Considered as a whole, the face is large and round, resembling a full moon," according to the descriptive report of Gull. "The lids are infiltrated and cover the eyes so that they appear smaller; the nose is enlarged, the lips thick and protruding, the forehead and the ears are wrinkled, the cheeks are puffed and flabby. This tumefaction of the face is associated with changes in the coloring; the skin has a yellow waxy pallor with a marked redness of the cheeks and a slight cyanosis of the lips. These changes cause the face to appear deformed and monstrous and give an appearance of stupidness which causes the condition to be characterized as cretinoid." (Souques).

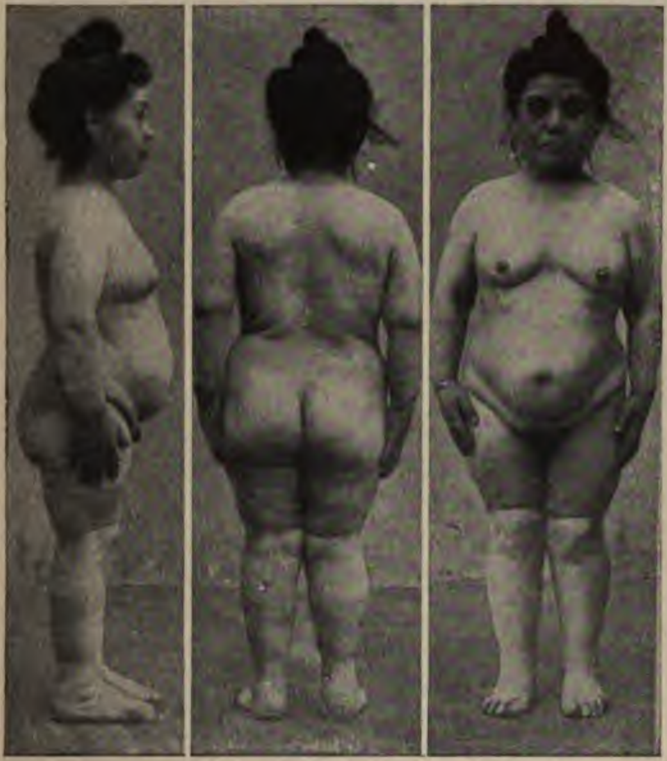


FIG. 1.—Myxedema (Infroid collection).

This infiltration is not only present in the face, but invades the whole body. The skin has a pale yellow appearance. The supraclavicular, axillary and inguinal hollows are filled in. The limbs appear to be infiltrated with a hard elastic edema, which does not keep the impression of the fingers. The hands and feet are enlarged and thickened and have a spade-like appearance. The fingers are thick, sausage shaped and cyanotic, and the patients have some difficulty in moving their limbs or performing delicate movements with their fingers.

The skin is not only infiltrated but dry and coarse (whence the name of pachydermic cachexia suggested by Charcot). Sweating is abolished. The hairs become dry, break off and fall out in the temporal occipital regions. There is often a falling out of the eyebrows, eyelashes and hairs of the arm pit and pubis. The nails become fragile and striated longitudinally.

Similar changes take place in the mucosa. The tongue thickens and moves with difficulty; the teeth loosen up in the tumefied gums; the voice becomes weak, due to the infiltration of the laryngeal mucosa.

2.—Atrophy of the Thyroid.—At the beginning it is possible to notice a transitory swelling of the thyroid preceding the atrophy. This occurs as a rule after a certain time. The infiltration of the tissues renders the palpation of the gland very difficult.

3.—Mental Changes.—The patient with myxedema is in a state of stupor and apathy; he stays motionless and isolated, indifferent to all that is going on; he avoids moving and walks very slowly. He is incapable of keeping his attention on anything or to exercise his memory. He looks stupid and answers questions in a slow and monotonous voice. Some cases have an unconquerable desire to sleep and do so anywhere.

4.—Secondary Symptoms.—These patients complain all the time of being cold; in winter they stay near the fire covered with blankets and their feet on hot water bottles; in summer they wear an excessive amount of clothes and stay in the sun all the time. Their body temperature is lowered and can be below 36° centigrade.

The heart sounds are muffled; the pulse is small and the blood pressure below normal. The reflexes are weak and the cutaneous sensation somewhat dulled.

Nutrition is slowed down, although the digestive functions are normal and the appetite is good; these patients have a dislike for meat. The urines contain very little urea or uric acid.

Genital disturbances are constant: in the male sexual frigidity is the rule. The majority of women with myxedema cease to menstruate; in some of them, however menstruation keeps up and an intercurrent pregnancy may bring about a temporary improvement of the symptoms of myxedema.

The examination of the blood reveals a certain amount of anemia; decrease in the red cells, and in the percentage of hemoglobin. An increase in the diameter of the red corpuscles and the presence of nucleated cells characteristic of the blood picture of children, is often noticed. (Vaquez).

2. MYXEDEMA IN CHILDHOOD.

This disease was described by Bourneville in 1880 under the name of *myxedematous idiocy*, and can be congenital or acquired.

1.—Congenital Myxedema.—It becomes evident from birth or a few months afterwards. It is due nearly always to an absence of the thyroid. If the gland does exist it is only made up of pea-shaped nodules. We do not know in the majority of cases the cause of athyroidism: tuberculosis, alcoholism, syphilis in the parents are the only hereditary stigma which occasionally are found.

The myxedematous new-born child shows a characteristic appearance, which enables us to make the diagnosis on first sight; the head is large, round, close to the shoulders; the forehead is low and narrow, the eyelids swollen, the nose short and broad, between two flabby cheeks. The lips are thick and droop. The tongue is enlarged, cyanotic and protrudes from the mouth, from which saliva drools all the time. The facial deformity gives an appearance of apathy and stupidity. The skin is pale yellow, thick and coarse to the feel.

The thorax seems crushed between the large head and the prominent abdomen. The skin of the thorax shows the same characteristic pallor and thickening; it forms rolls and wrinkles in the flanks.

The limbs seem enormous, especially at the level of the hands and feet which are thickened cyanotic and infiltrate with an indurated edema.

The hairs are dry and break easily; the nails are striated and badly formed; the voice is hoarse and nasal.

The examination of these patients reveals a defective nutrition and circulation; the pulse is small, imperceptible; the respiration short; the body temperature below normal: 35 or 36 degrees centigrade.

Coming on at an age when the body is in process of growth and when the intellect is not yet developed, congenital myxedema causes a complete arrest of both physical and mental development; whence the two important diagnostic signs: *dwarfism and idiocy.*

The height and weight are much inferior to the normal; the first teeth appear late; the fontanels stay open until an advanced age.

Idiocy is absolute: the child cannot stand or walk; he stays still in a chair and lets known by cries when he is hungry or thirsty. He is not able to feed himself. He is a plant, which simply breathes and digests. Very late he finally learns to walk, but his movements are very slow. He never is able to learn to talk or write; all attempts to educate him are a failure.

The evolution is very slow, without any spontaneous improvement. If the child reaches the age of puberty, the physiological changes of this period do not appear; the genital organs stay infantile and the hairs do not grow either in the axilla or the pubis. These subjects have a very poor resistance to infections and usually die of some intercurrent disease or of tuberculosis. It is very rare to see a case of congenital myxedema over 30 or 40.

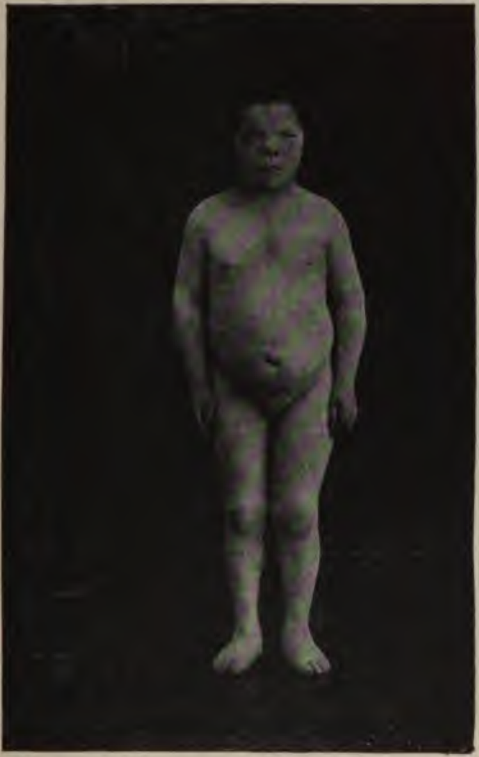


FIG. 2.—Myxedematous dwarfism (Infroid collection).

2.—Acquired Myxedema.—It occurs usually in the first part of childhood. The usual cause is some infectious thyroid lesion, secondary to measles, scarlet fever, broncho pneumonia, gastro enteritis, etc. (Roger and Garnier).

The symptoms are the same as those of the congenital type, but less severe. The physical development is better and the mentality more advanced; dwarfism is less marked and the idiocy less absolute. As a general rule, the symptoms of myxedema are proportionally less pronounced as the disease occurs later in life.

The skin is still thickened and infiltrated, but much less dry. The first teeth come out at the normal time, but the second crop does not appear or the teeth are badly developed. Growth is delayed, the height is below the normal for the age. Ossification is not completed.

The mentality is not retarded as much and these individuals can be educated to a certain extent; motion is very slow and awkward, but they can make themselves understood and can obey a few simple commands. The low body temperature, the sensitiveness to cold are as appreciable as in the previous type. These children when untreated usually die early.

3. POST OPERATIVE MYXEDEMA.

In 1882 *J. Reverdin* showed that the affection described by Gull in adults and by Bourneville in children, could occur in either case after a thyroidectomy for goitre. This was a very important discovery which led to the pathogenic treatment of myxedema; thyroid organo therapy.

The total extirpation of goitres or a total thyroidectomy causes in man, as well as in animals, two kinds of phenomena.

1.—ACUTE SYMPTOMS which were studied under the name of acute post operative myxedema. These were in reality cases of tetany due to the simultaneous extirpation of the thyroid and parathyroids.

2.—CHRONIC SYMPTOMS.—These occur usually three or four months after the complete thyroidectomy (partial thyroidectomy only causes mild and very transitory symptoms). The clinical picture is identical to that of acquired myxedema of the adult; infiltration, anemia, loss of hairs, asthenia, with slowness and awkwardness, sleepiness, deterioration of mentality and low body temperature.

In children the symptoms are more marked than in adults. The thyroidectomy brings on a complete stoppage in mental and physical growth, being the more marked as the subject has been operated on early in life.

3.—Endemic Myxedema or Cretinism.—Cretinism is found in certain mountainous countries (Valois, Alps, Pyrenees) in children drinking water from certain springs, and is characterized by a physical and mental deterioration. This condition is so similar to the myxedematous idiocy that the only way it can be differentiated from it, is by the presence of a goitre. The latter develops as a rule around puberty and becomes enormous. It forms sometimes a hard tumor, containing cartilagenous centres, at other times, soft or cystic tumors. In spite of the presence of the goitre the function of the thyroid is abolished. According to their mental state these cases are classified as complete cretins, in which walking can only be accomplished on all fours and speech is replaced by noises and semi cretins and cretinoids in which speech is slow but who, however, are able to perform a few simple tasks.

4. ABORTIVE MYXEDEMA.—CHRONIC MILD HYPOTHYROIDISM.—SLIGHT THYROID INSUFFICIENCY.

When lesions of the thyroid disturb, without abolishing the function of the gland, myxedema reveals itself in a series of types showing various grades of thyroid insufficiency.

A. IN CHILDREN.

Following an infectious disease, the child shows a retardation in development. The skin becomes thicker, but not as much as in typical myxedema. The face is slightly pale and puffy and the rest of the body shows a slight obesity which tends to hide the sexual characteristics.

Young boys show excessive adiposity, most marked at the level of the hips and the breasts. Little girls show an ungraceful obesity: the breasts are invaded with fat, the abdomen bulges out, the skin forms pleats on the sides and on the abdomen.

At a more advanced age thyroid deficiency causes myxedematous infantilism. This attenuated type of myxedema, described by Brissaud, is evidenced by the morphological signs of childhood after puberty. The face is round, the thorax is elongated and cylindrical, while the abdomen protrudes as in childhood. The limbs are rounded. The shape is feminine, the underlying muscles being hidden by an excessive amount of subcutaneous fat. The genital organs are rudimentary; the penis is small and short; the testicles are well formed, have descended, but are small. The hairs are few or even absent on the pubis, axilla and face. The voice remains high pitched; the larynx does not protrude. In the female, the pelvis and the breast do not develop. The vulva looks forward as in little girls and menstruation does not appear.

X-ray of the skeleton shows a delay in the appearance of ossification points and persistence of cartilage outside of the normal limits. Adolescents are like big children, not only physically but mentally. They are emotional, easily frightened, without care and are very affected.

All cases of infantilism are not myxedematous and this type must not be mistaken for the real infantilism of Lorain. The latter is characterized by a decrease in size. The morphology is, however, not that of a child. The features of the face are formed; the shoulders are large and proportional to the other parts of the body. The abdomen is not prominent; the musculature can be made out. The sexual organs, while reduced in volume, are harmonious with the rest of the organism. The cartilages are fixed. There is no mental backwardness. To give the description of Meige, these cases are miniature men. Baur has designated these cases under the name of chetivism. This description allows us to understand the difference between the infantilism of Brissaud and that of Lorain.

B. IN ADULTS.

The symptoms of abortive myxedema studied by Thibierege are even more marked than in childhood.

The complexion is yellow; the eyelids are puffy, particularly in the morning. The hair turns gray early and falls from the forehead and the top of the cranium. The eyebrows are scarce, the mustache is scanty, the beard grows unequally, the hands and feet show an indurated edema and appear swollen and often show signs of vaso motor disturbances: acrocyanosis, syndrome of Raynaud, etc. The skin of the extremities is dry, coarse, thick and scaly, sometimes having the appearance of ichthyosis. The individual has a tendency to obesity. The pulse is weak and the blood pressure is low.

Hertoghe, then L. Levi and H. de Rothschild, have described a certain number of minor signs which are evidences of thyroid insufficiency. The most important are the following:

1.—Calorific Disturbances.—Cases of hypothyroidism are very sensitive to cold. Not only do they have cold extremities, but they feel the desire to warm themselves up and cover themselves excessively at night. Their body temperature is, moreover, often below normal. Sometimes towards 4 or 5 o'clock they have chills, particularly in the region of the back (Hertoghe).

2.—Nervous Disturbances.—These patients complain of a sensation of fatigue in the morning, and only begin to feel normal after having been up for several hours. They complain of frontal or occipital headaches, muscular and articular pains, vaguely called neuralgias and of indefinite etiology. In some there is a decrease of the memory and of physical activity, resembling neurasthenia or psychasthenia. Others need considerable sleep and doze off after each meal. Some have a marked intellectual apathy.

3.—Edema.—White, firm, indolent edema, independent of all cardiac or renal affection, occurring on the face (forehead, eyelids). Some women at the time of menstruation have a temporary swelling of the hands and feet and can only remove their rings with difficulty.

4.—Digestive Disorders.—Outside of anorexia, a common symptom, there is often, in women, a persistent constipation with or without muco-membranous colitis.

5.—Piliary Disturbances.—Early baldness, alopecia, associated with rarefication of the hairs of the outer part of the eyebrows are stigma of thyroid insufficiency.

Cases of hypothyroidism are predisposed to a variety of morbid disturbances.

Respiratory infections are frequent in these patients which often have hypertrophic tonsils, a red pharynx, retracted nasal fossea, due to thickening of the mucosa. They are subject to repeated sneezing (Hertoghe) to sore throat, colds in the head and bronchitis. Asthma, of nasal origin is often remarkably improved by thyroid organo therapy.

Menstrual disturbances are nearly constant and show themselves at the time of the periods by real hemorrhages, others have painful menstruation accompanied by headache or excessive nervous irritability.

The attacks of migraine also come on between the periods. Their thyroid etiology is proved by the fact that they are rapidly improved by thyroid medication and that an intercurrent pregnancy or the menopause causes them to disappear due to the overactivity of the thyroid during these periods of sexual life.

Finally, many conditions have been found to be due to hypothyroidism, such as: urticaria, eczema, psoriasis, etc., chronic rheumatism under a variety of aspects even the progressive deforming type.

These various manifestations due to thyroid insufficiency are found to be related to this condition, not so much by their clinical appearance as by the co-existence of various stigma of hypothyroidism. We are entitled to suspect hypothyroidism when after the examination of a patient several symptoms of hypothyroidism have been detected and to verify our diagnosis by a therapeutic test.

We must not expect to find in one patient all the signs of hypothyroidism. Some patients only show a yellow skin and a slight infiltration of the tissues. Others are simply stout without any other signs. Furthermore, the physical stigma have a much more valuable diagnostic significance than have functional manifestations; such as, fatigue, headache, constipation. If we suspect such common symptoms to be all due to hypothyroidism, the majority of medical diseases would have to be treated by the administration of thyroid.

TREATMENT OF MYXEDEMA AND OF THYROID INSUFFICIENCY.

A. MYXEDEMA.

We will only refer to thyroid gland grafts; the first attempts made in France were by Lannelongue and did not succeed. Kocher and Payr only obtained temporary results, because of the total resorption of the gland. In spite of a few successful cases reported by Charrin, Christiani, Gauthier, etc., who grafted in the subcutaneous cellular tissue small fragments of thyroid, the method has not become generalized.

To-day, thyroid organo therapy is the only method employed.

ORGANO THERAPEUTIC PRODUCTS.—Thyroid is usually administered by mouth as the dried extract, fresh gland or iodothyrin.

a—The fresh gland is a very active medication, but can only be used absolutely fresh. Sheep's gland is used, the average dose being between 1.5 grammes to 3 grammes in adults (or 1 or two lobes), 0.25 to 1.5 grammes in children. It is given raw, spread on toast or chopped up and mixed with milk, or slightly warmed up soup. In certain cases of congenital myxedema who swallow with difficulty, it is possible to administer thyroid, chopped up very finely, in an enema.

b—The dried gland as a powder, prepared in a vacuum and in the cold is the best preparation to use, because of its ease of administration. The average dose is from 0.3 to 0.4 grammes.

c—Iodothyrin is one of the active principles of the thyroid and is given in doses of 0.25 to 0.75 daily.

METHOD OF ADMINISTERING THYROID MEDICATION.

1—It is first necessary to find out gradually the susceptibility of each patient and begin with small doses (¼ of a lobe or 0.05 grammes of the dried powder in a child, ½ lobe or 0.1 grammes in an adult) and slowly increase the dose.

2—The treatment may have to be kept up a few months, a few years and perhaps all the life of the patient, if recurrences are to be avoided. In children just as large doses can be used as in adults, for observation has shown that they tolerate thyroid extract very easily.

3—Once the results are obtained, the treatment is to be discontinued. Smaller quantities are to be used, varying with each individual and the patient is advised to take the medication for three weeks and then abstain for one week, or again he may be told to take the medication one week and rest the next.

Results of the Treatment.—Thyroid medication is indicated in all the forms of myxedema. It will always bring about some improvement and may even cause a cure.

The results are the more marked as the child is younger; the infiltration of the tissues decreases rapidly and a real physical transformation occurs. The skin loses its roughness, the hairs become less coarse and grow longer, the features become more refined. The weight decreases and the height increases. The intellect improves, following the physical transformation. The indications for treatment can be very easily regulated by the measurements. As soon as growth ceases and weight increases, the treatment is to be taken up again.

In older children, the delayed growth is resumed under the influence of the treatment. Due to the persistence of cartilage, these individuals can still increase in size at an age when growth has ceased in normal subjects. They become susceptible of an elementary education and in a few months the changes may be complete.

In adults the therapeutic results are less marked.

B. THYROID INSUFFICIENCY.

The majority of the symptoms and accidents due to hypothyroidism, obesity, migraine, menstrual disturbances, constipation, etc., are attenuated under the influence of organo therapy. In general, however, the improvement is only temporary and ceases after the suppression of the medication. In chronic rheumatism the results are proportionately more successful as the rheumatism is recent and the subject is young.

The administration of thyroid in these cases is more difficult. All authorities agree on the necessity of slowly finding out by experimentation. Very small doses must be used at first (0.01, 0.025 milligrammes) as these doses will in some cases be sufficient to cause an improvement. If the improvement does not manifest itself, then larger doses are used, which in certain individuals might cause symptoms due to hyperthyroidism.

It is also advisable to discontinue the treatment occasionally and have periods of treatment followed by rest periods, so as to avoid accumulative effects and intolerance.

The good effects of organo therapy do not occur. sometimes for quite a long period of time. The treatment should, therefore, be continued in certain unimproved cases for several months or even years.

ACCIDENTS OF THYROID MEDICATION.—SIGNS OF INTOLERANCE.

The use of thyroid medication, because of its potency should be watched. The extract of thyroid has a definite action on the cardiac rythm and the arterial pressure. Experimentally, it causes an acceleration of the heart rate and a characteristic drop in blood pressure. Collapse and even sudden death have been reported following its use in individuals with degeneration of the myocardium or valvular lesions. It is, therefore, important to test out with small doses at the beginning of treatment.

During the course of the treatment, the intolerance manifests itself by the following symptoms: Acceleration of the pulse, palpitations, heat waves, sweating, tremors, loss of weight, diarrhea. As soon as they appear the medication should be discontinued or at least considerably reduced. These symptoms of intolerance are more frequent in adults than in children.

THE SYNDROMES OF HYPERFUNCTION OF THE THYROID.

I. EXOPHTHALMIC GOITRE.

Exophthalmic goitre is a disease characterized by the following signs: hypertrophy of the body of the thyroid, exophthalmos, tachycardia and tremors. To these are added a number of secondary signs, the majority of nervous origins, which give quite a peculiar appearance to this disease.

It is also called Basedow's disease in spite of the fact that this condition was first described by Flajani in Italy and afterwards by Parry and Graves in England.

It occurs most often in women between the ages of 20 and 40, usually associated with a nervous stigma or an impressionable character.

SYMPTOMS.

They begin very slowly and very progressively. The first noticed are nervous manifestations. The patient becomes peculiar and irritable. Her immediate friends notice a change in the patient. She complains of waves of heat, flushes, palpitations, insomnia. On casual examination a swelling of the thyroid is noticed and an acceleration of the pulse rate. Very often this condition is interpreted as hysteria or nervousness.

Slowly the characteristic signs of the disease become prominent.

1.—TACHYCARDIA.—This is a very important sign, as it appears early and is very constant. The patient complains after the slightest effort, or the least excitement, of palpitations, at first intermittent and in the end constant. During the day time they sometimes have a sensation of discomfort which is very painful; at night they complain of palpitations and sleep poorly.

The pulse is rapid; 90 to 120 per minute. It is small, but generally regular, although in some cases it can be very variable. Following a slight effort or excitement, it will go up to 100, 150, or 180. This acceleration of the pulse occasionally occurs spontaneously and coincides with attacks of palpitation. Quite often there is a slight rise in blood pressure.

The examination of the heart reveals an abnormal cardiac condition. The wall is pushed forcibly at the apex and can be easily palpated. Auscultation reveals a tachycardia, either simple or associated with extra cardiac murmurs. If organic murmurs are present, these are probably due to some previous rheumatic endocarditis (Barie).

2.—THE GOITRE.—Very soon the volume of the thyroid increases, obliges the patient to wear larger collars or a more opened waist. Sometimes under the influence of fatigue or menstruation it grows very rapidly and in the interval goes down slightly.

At an advanced period the hypertrophy of the gland causes a deformity of the neck, generally asymetrical. The right lobe being nearly always the largest. The vessels of the neck pulsate and are plainly visible, this in contrast to the very small pulse (Graves). These pulsations are limited to the carotids.

Exophthalmic goitre is a vascular goitre. On palpation it is elastic and semi soft; occasionally it gives a sensation of a thrill or of expansion synchronus with the cardiac systole. On auscultation a hum is often heard, most pronounced in systole.

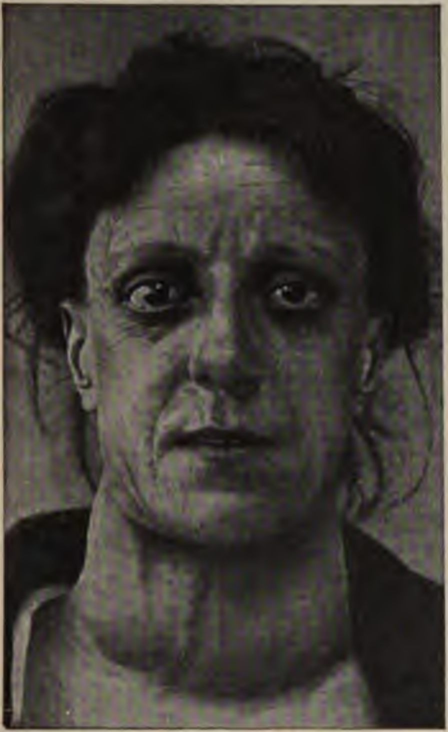


FIG. 3.—Exophthalmic goitre (Service of Dr. Florand).

Some patients tolerate this hypertrophy perfectly. Others have a painful contraction of the larynx. The recurrent laryngeal nerve can be compressed; in which case the voice becomes hoarse.

3.—EXOPHTHALMOS completes the picture. The eyeballs protrude, and the lids are wide open, giving an expression of fright. In most cases it is symmetrical, but sometimes starts in one eye before becoming noticeable in the other. Very rarely it stays unilateral, coinciding with a thyroid hypertrophy on the same or opposite side.

The protrusion of the eyes may become so prominent that the insertion of the anterio ocular muscles is visible, and interferes with the closure of the eyelids and exposes the cornea to infection.

Emotions, fatigue, menstruation, increase exophthalmos just as they do the goitre.

As a rule the patients do not have any visual disturbances, except a certain difficulty in fixing objects or reading small print.

The pupils are equal, usually with a slight mydriasis and react quickly to light and accommodation. Paralysis of any of the extrinsic muscles is exceptional.

Next to ophthalmia we have a number of signs indicating an absence of coordination between the movements of the eyelids and those of the eyeball. They are as follows:

1.—Von Graefe's Sign.—The movements of the lids lag behind those of the eyeball. When the patient looks downwards the superior eyelids do not follow it completely and the eyeball stays abnormally open.

2.—Boston's Sign.—The eyelids follow by jerks the ocular movements.

3.—Stellwag's Sign.—When the lids try to close, the pupil hides under the superior lid instead of the latter coming down.

4.—Joffroy's Sign.—The frontal muscle does not move when the patient looks upwards (due to lack of synergy between the movements of the frontal muscle and the levator palpebrarum). Other signs not as common:

5.—*Moebius' Sign*—The eyes converge with difficulty, due to paresis of the internal recti.

6.—*Jellenick's Sign.*—Abnormal pigmentation of the eyelids and of the skin of the orbit.

4.—Tremor.—The last of the important diagnostic signs. It may be localized to the legs or generalized with predominance of the hands and head.

The following are its characteristics: 1.—Fine tremor of small amplitude. 2.—Mixed tremor both spontaneous and intentional, not modified by the will. 3.—Tremor increasing in intensity after fatigue and excitement.

The tremor can be brought out in the following manner: 1.—At the level of the head by a piece of paper on the top of the head.

2.—Of the superior limbs by having the patient raise his hand as if taking an oath; the tremor does not stay localized to the fingers as do alcoholic tremors, but involves the hand, the muscles of the forearm and even in some cases the arm.

3.—At the level of the thorax, by placing a hand on each shoulder a continuous vibration may be elicited.

4.—Of the inferior limbs, the patient sitting down, with his feet resting, moves the tips of his toes (P. Marie).

To these functional signs are added other symptoms which have not the same constancy or the same clinical value. The majority are indicative of a secretory disturbance of the thyroid or of some other gland of internal secretion. They vary with each patient and affect different systems.

1. NERVOUS DISTURBANCES.

a.—Disturbances in motility. These consist of muscular cramps, particularly in the calves of the legs, contractures and even epileptiform attacks.

When paralysis occurs, it usually is localized to the legs and at the beginning shows the characteristic of a paraplegic functional paralysis with sudden onset and with the retention of the reflexes and integrity of the sphincters (Paraplegia of Basedow's disease described by Charcot).

b.—Sensory disturbances. These vary; neuralgia in various localities (cervical, occipital and especially facial) or arthralgia simulating rheumatism.

c.—Secretory and vaso motor disturbances. These are very common and very important; waves of heat, profuse sweating, generalized or localized to the neck, trunk, arms, etc; sensation of abnormal heat or thermophobia. The patients place themselves in a draft or sleep without any bed clothes in winter.

d.—Dystrophic disturbances. These are present in certain subjects. In some cases there is a melanodermia resembling Addison's disease, vitiligo, brown spots, edemas characterized by a thickening of the skin at the level of the neck and buttocks.

e.—Psychic disturbances are nearly always present.

Changes in character become more pronounced as the disease evolves. The patients are impatient, emotional, irascible; one minute sad, the other cheerful and become very unsociable because of their change of humor. In predisposed individuals these changes may result in a true psychosis, melancholia, mania, with hallucinations, or persecution. etc. Insomnia is frequent. This can be opposed to the sleepiness of myxedematous patients.

2. GASTRO INTESTINAL DISTURBANCES.

The appetite varies, sometimes increased, at others decreased. The digestive functions may be normal. Occasionally, patients with Basedow's disease have gastro intestinal crises, beginning and ending very suddenly and resembling tabes; ptyalism, gastric or abdominal crises with vomiting and attacks of diarrhea, containing mucus and bile and which exhaust the patient and are followed by a marked loss of weight.

3. RESPIRATORY DISTURBANCES.

Outside of the rare cases in which a large goitre presses on the air passages and causes respiratory difficulties, certain individuals with only a small goitre, have a dry cough, coming on in paroxysms and spasmotic in character.

The respiratory difficulty in some cases consists of a difficulty in dilating the thoracic cage and taking a deep breath (Bryson).

4. GENITAL DISTURBANCES.

The genital disturbances are constant in Basedow's disease.

In man there is frigidity or impotence. In women the menses are irregular or may be absent and then re-appear. The breasts nearly always become atrophic.

5. URINARY DISTURBANCES.

Polyuria occurs at intervals very much like the attacks of diarrhea.

During the periods in which the goitre is growing rapidly albuminuria and even glycosuria can be noticed. This glycosuria seems to be the result of hyperthyroidism.

6. GENERAL SYMPTOMS.

Fever is not exceptional in Basedow's disease. It occurs at intervals and lasts for a variable length of time.

The examination of the blood shows a leukopenia with lymphocytosis (Kocher). These blood changes are very constant and are also found in the abortive cases.

EVOLUTION.

Basedow's disease may evolute very quickly. It may develop after a fright. The sudden increase in the volume of the thyroid causes asphyxiating symptoms, associated with cyanosis suffocation, often made worse by an associated enlargement of the thymus. It may improve and be the starting point of a slow evoluting type of case.

In the majority of cases the evolution lasts for years, and progresses by sudden periods of activity during which the chief symptoms increase in intensity and are separated by intervals of remission or even regression which last a variable length of time.

The general health for a long time stays unimpaired. In spite of the fact that these patients have a good appetite, some of these patients lose weight for weeks or months at a time. These periodic spells of loss of weight occur without any apparent cause or after diarrhea; between these periods they regain weight. In this manner, the evolution is very slow.

Cure is very frequent. It may occur spontaneously, but in the majority of cases is rarely complete. The secondary symptoms decrease and may disappear, but exophthalmos, thyroid hypertrophy and tachycardia persist and recurrence is to be watched for.

In other cases, the condition grows worse after several exacerbation.

The patient dies from tuberculosis, progressive cachexia or from cardiac complications.

1.—PLEURO-PULMONARY TUBERCULOSIS in one of its various forms is a frequent complication.

2.—CACHEXIA characterizes certain cases. They have anorexia, incoercible vomiting, profuse diarrhea, albuminuria and in spite of the absence of any evidence of tuberculosis are reduced to skeletons. Some become cachectic in a few weeks without diarrhea and die of marasmus.

3.—Cardiac Disturbances.—Certain cases of exophthalmic goitre have a marked paroxysmal tachycardia. Others, as a result of fatigue, have an acute dilatation of the heart, an extreme dyspnea and die of asphyxia. In others, cardiac insufficiency develops slowly: edema, oliguria, and albuminuria and symptoms of dilatation of the right heart with foci of pulmonary apoplexy showing the typical picture of progressive asystole. This has usually a valvular lesion as a starting point, resulting from a previous attack of rheumatism (Barie).

CLINICAL FORMS.

Exophthalmic goitre shows certain peculiarities.

1.—In Children.—The condition can be hereditary or familial. It is mostly found in girls. The symptoms are mild; the goitre is not very big; the exophthalmos not very pronounced or absent; the tremor less marked and sometimes resembles chorea. A cure is possible, but a recurrence must be watched for when the patient grows up.

2.—In Man.—When Basedow's disease occurs in man, the nervous symptoms and in particular the psychic symptoms are very marked and appear long before any of the important diagnostic signs. The evolution is more rapid and the prognosis is bad (Pic and Bonnamour).

3.—In Pregnant Women.—Pregnancy is rare in this condition, as exophthalmic goitre is often accompanied with atrophy or insufficiency of the ovary.

Some cases, however, are able to have several pregnancies without any trouble. Furthermore, it may be a cause for improvement. In other cases, however, pregnancy occurring during the course of Basedow's disease has very dangerous consequences. It causes abortion, hemorrhages and even cardio pulmonary complications which resemble the severe gravid cardiac accidents.

4.—ABORTIVE TYPE.—Charcot and his pupils, Pierre Marie among these, have shown that next to the typical types of these affections mild or abortive cases exist.

According to P. Marie, the fundamental symptom of Basedow's disease is tachycardia, and goitre, exophthalmos and tremor may be missing.

The abortive cases are characterized by tachycardia, either with exophthalmos without a goitre, or with a goitre and no exophthalmos, or finally alone. The vaso motor, nervous, psychic changes which accompany these mild cases are sufficient to relate it to exophthalmic goitre. Next to these mild cases, we must place various cardiac neurosis. In certain defectives, having no signs of Basedow's disease, not even a goitre, fatigue or excitement cause palpitations and tachycardia, a cardio vascular and nervous instability and even a slight tremor. Certain cases of tachycardia, not well classified, occurring intermittently and in paroxysms, which we saw during the war were probably due to disturbances in the thyroid function. These cardiac neuroses are closely allied to attenuated cases of Basedow's disease and there is no definite line of demarcation between them.

5.—ASSOCIATED FORMS.—Basedow's disease is liable to co-exist with different nervous affections of the nervous system: syringomyelia, epilepsy, general paresis and particularly tabes. In the latter case it is probably of luetic origin.

Combinations with other glandular syndromes are very curious: acromegalia, gigantism, Addison's disease, myxedema, etc. The latter follows the goitre in certain cases following radiotherapy or the two affections evolute together.

Finally, exophthalmic goitre can exist with a number of diseases, the glandular origin of which is suspected but not proved; diabetes (severe diabetes with abundant glycosuria), Dercum's disease, paralysis agitans, sclerodermia, Raynaud's disease, osteomalacia, tetany, myasthenia, etc.

DIAGNOSIS.[1]

1.—The diagnosis of typical Basedow's disease is made; when the four cardinal symptoms have been observed; this is found only in this disease. If the exophthalmos is very mild and if the ocular symptoms consist simply in a certain fixity and peculiarity of the eye, bulbar tabes can simulate the syndrome of Basedow's disease by ophthalmoplegia and tachycardia. The examination of the patient reveals, however, the presence of symptoms of tabes foreign to Basedow's disease. A co-existence of the two diseases is however possible.

2.—In mild or abortive form the diagnosis is difficult. In these cases the tachycardia predominates and the other symptoms are practically absent. Certain cases of Basedow's disease appear clinically to simulate tuberculosis, cardiac diseases, or nervousness.

a.—Pseudo tuberculosis, because they have a dry cough, a rapid pulse, diarrhea, sometimes fever and they lose weight.

b.—Pseudo cardiac, because they complain of palpitations, and they have extra cardiac murmurs. Some have pain which simulates angina pectoris, others have paroxysms of tachycardia and palpitation resembling paroxysmal tachycardia.

c.—Pseudo nervous, because they complain of a variety

GOETCH TEST FOR HYPERTHYROIDISM.

[1] The subcutaneous injection of ½ c.c. of 1-1000 adrenalin solution will cause a rise of blood pressure of over 10 mm. or an increase of pulse rate of over ten beats a minute

of symptoms; vaso motor, dyspeptic, etc., which add to their mental state. Their impressionability often leads us to suspect neuropathy or hysteria.

The cardio vascular disturbances must be looked for carefully, the instability, the hyperexcitability of the pulse, which increases at the slightest effort should lead us to suspect a thyroid lesion. The therapeutic test may be of great help: antithyroid medication may improve the case while thyroid medication, even in small doses exaggerates the symptoms of this morbid condition.

ETIOLOGY.

Basedow's disease is often the late sequel of an infectious disease: an acute thyroiditis caused by typhoid fever, scarlet fever, mumps, particularly acute articular rheumatism. It can also be the result of a chronic tuberculous or syphilitic thyroiditis.

In certain cases it seems to be the result, as in some cases of diabetes, of a cranial trauma.

It may begin very rapidly, following violent emotions, fright, moral shock, repeated and deep sorrows.

Some cases of exophthalmic goitre appear without any apparent cause.

PATHOLOGICAL ANATOMY.

There are no specific anatomical lesions of Basedow's disease.

The thyroid is increased in volume as a whole, the right lobe being usually larger than the other. The thyroid veins are dilated and filled with blood. The gland is of soft consistency, and of a dark brown color. When incised, it often contains cysts filled with colloidal substance. The histological lesion, according to the investigations of Callum, Roussy and Clunet, resemble the compensatory hypertrophy obtained experimentally after the removal of the greater part of the thyroid and show definitely a hyperfunction of the gland: hypertrophy and parynchymatous hyperplasia with increased colloid secretion. The colloid is paler, less chromophilic and more friable than normally. The abnormal cellular proliferation is characterized by masses of eosinophils. The thyroid follicles are dilated and are shown surrounded by fibrous tissue, more or less abundant and containing lymphoid cells.

Lesions of the cervical sympathetic are rare. In some cases the nerves are increased in volume and sclerosed; the inferior cervical ganglion contains atrophic cells, smothered by a proliferation of connective tissue.

Lesions of the nervous system (bulb and cord) are exceptional and when they do exist do not have any specific appearance.

It is quite common to see an increased activity of the thymus in cases of exophthalmic goitre.[1]

PATHOGENESIS.

In spite of numerous theories, the definite pathogenesis of Basedow's disease is still undetermined.

1.—NERVOUS THEORY.—The syndrome is produced by a lesion of the cervical sympathetic (Abadie). The stimulation of the sympathetic causes tachycardia, exophthalmos, dilatation of the arteries of the thyroid. Secondarily, the thyroid hypertrophies and due to a functional hyperactivity, pours into the blood stream toxic substances which cause the secondary symptoms: tremor, diarrhea, loss of weight, etc.

2.—THYROID THEORY.—(*a*) Hyperthyroidism. Basedow's disease is the result of a hyperthyroidism (theory of Moebius). Experimental, clinical and therapeutic observations have shown the exaggeration of the thyroid secretion: the symptoms of myxedema characterized by atrophy of the gland are opposed to those of Basedow's disease. Experimentally, the injection of excessive doses of thyroid extract reproduces in animals some of the symptoms of the disease: tachycardia, loss of weight, as Basedow's disease is improved by anti thyroid medication.

---

[1] This may account for the ovarian and genital atrophy.

The following facts are, however, opposed to the conception of hyperthyroidism: myxedema may co-exist with Basedow's disease. Gley has also shown that the serum of patients with Basedow's disease has not the experimental effects of the extracts of thyroid and that the intravenous injection of extract of exophthalmic goiter causes a decrease in the blood pressure, a decrease in the strength in the heart beat, just as would the extract of a simple goitre.

(*b*) Dysthyroidism (theory of Gauthier and Charolles, then of Renaut and Joffroy, brought up to date by Gley and Iscovesco). The symptoms of exophthalmic goitre are brought about by a perversion of the thyroid secretion causing an accumulation in the blood of toxic substances, normally destroyed by the thyroid. Perhaps one of these substances, stimulating the sympathetic is normally fixed by the thyroid. The tachycardiac and the exophthalmos could be understood without a lesion of the sympathetic.

3.—POLYGLANDULAR THEORY.—The disturbance in the thyroid secretion is not primary, but secondary to the functional alterations of another gland in synergy with the thyroid, whence the thyro-ovarian and thyropituitary theories. The thyro adrenal theory is upheld in Germany and in America, by Wilson. Hyperthyroidism causes a hyperfunction of the adrenals, which causes a hypersecretion of suprarenalin, a permanent stimulant of the sympathetic.

II. THE VARIOUS BASEDOW'S DISEASE SYNDROMES.

To the typical Basedow's disease are related a number of clinical syndromes of various etiology. These syndromes are related to the existence of a goitre. They are also secondary to the ingestion of thyroid products or of iodides. They may also be of ovarian origin.

1. *Pseudo* EXOPHTHALMIC GOITRE.

Certain goitres compress the cervical sympathetic on one or both sides and cause an exophthalmia, associated with an acceleration of the heart without any other sign of Basedow's disease.

There are simple goitres which for years evolute without any disturbance; then under the influence of overwork or sorrows or following the administration of iodides, sometimes even without any evident cause show evidence of Basedow's disease. In these cases not only is exophthalmos and tachycardia noticed, but signs of thyroid intoxication: tremors, vaso motor disturbances, psychic changes diarrhea, etc.

These can be differentiated from the classical Basedow's disease by the following characteristics: the goitre has been perfectly well tolerated for a number of years, the palpation of the thyroid reveals at least in one of the lobes the presence of cartilagenous or fibrous masses, while true exophthalmic goitre is a soft goitre and is essentially vascular. Surgical treatment improves or cures these cases.

Certain cases of cardiopathy, associated with goitre, can be classified very closely to Basedow's disease. Some patients with a simple goitre show prominent cardiac symptoms; in some the symptoms are those of cardiac insufficiency, complicated with pulmonary stasis secondary to pulmonary lesions of bronchitis with emphysema.

They are found in cases of goitre in which the respiratory passages are compressed by the hypertrophied thyroid.

In others, the cardiac manifestations are independent of all pulmonary affections. The goitre varies in size; in some cases it is even small, retro sternal and can be even overlooked, while the patient complains of violent palpitations, coming on spontaneously or after the slightest effort. The heart is enlarged and beats between 100 and 140 and becomes accelerated and arythmic at the slightest provocation. More dangerous symptoms, in particular pains simulating angina pectoris, sometimes occur.

Asystole is the usual result of these cardiopathic goitres. Sometimes it is possible in these cases to note simultaneously a slight exophthalmos and a peculiar brilliancy of the eyes. According to Kraus, the removal of the goiter causes the disappearance of these symptoms. For these reasons, these cases are considered as abortive cases of Basedow's disease.

II. BASEDOW'S SYNDROME FOLLOWING THE INGESTION OF THYROID OR IODIDES.

In patients taking an excessive quantity of thyroid or following a course of thyroid medication for too long a period of time (for instance in the treatment of myxedema, or for stout women to reduce without proper medical supervision) the syndrome of Basedow's disease may appear more or less distinctly with tachycardia, exophthalmia, tremor, restlessness, nervosity, insomnia, etc.

This syndrome is usually temporary and will disappear after the removal of the cause. Similar symptoms may be seen in patients with simple goitres which have been given iodides.

3. SYNDROME OF BASEDOW'S DISEASE OF OVARIAN ORIGIN.—In certain young girls at the time of puberty,

in women at the time of the menopause, or after ovarectomy, the symptoms of Basedow's disease, in general attenuated, will appear. They are characterized more by a brilliancy of the eyes than by a true exophthalmos, a swelling of the thyroid, an acceleration of the pulse, and tremor. Ovarian organo therapy cures or improves these cases.

III. HYPERTHYROIDISM SIMULATING BASEDOW'S DISEASE.

This bears the same relation to Basedow's disease as slight hypothyroidism bears to myxedema.

The women suffering from this affection have characteristic appearance: The eyes are bright, the thyroid is slightly enlarged, they complain of palpitations of the heart during the day or the night, which last a few minutes. These symptoms are usually accompanied by a sensation of strangulation or waves of heat, followed by sweating. These women are usually very active, and constantly want to be on the move. Some have an exaggerated emotionability. Others are irascible. This condition is congenital and is more the normal condition of the patient than a disease.

The symptoms of hyperthyroidism appear after sorrow, overwork, emotions or even slight annoyances. The palpitations increase in intensity and become painful and are accompanied by a sensation of constriction of the thorax and sometimes a fear of death. The nervous disturbances become exaggerated: tremor, insomnia, abnormal excitability. All these symptoms very closely resemble Basedow's disease.

Between Basedow's disease and predisposition to Basedow's disease, characterized by cardio vascular instability and nervousness, we have no definite demarcation.

TREATMENT OF EXOPHTHALMIC GOITRE AND HYPERTHYROIDISM.

The proposed medications are numerous. After having described them, we will study their indications.

I. HYGIENIC AND DIETETIC TREATMENT.

A quiet life, without any emotions or fatigue, is essential to these cases. Absolute rest in some cases is sufficient to modify the tachycardia and the nervous symptoms.

The seashore is unadvisable, while the mountains, at a low altitude, are better tolerated. A stay at some mineral spring is a useful adjunct to the treatment. The sedative springs of Bourbon Lancy and of Neris (in France) are the ones which seem to benefit the patients most.

The food must be carefully watched: all stimulants, all toxic foods are to be avoided. It is advisable to weigh these patients, for a gain in weight is an indication of improvement.

II. MEDICAL TREATMENT AND ORGANO THERAPY.

1.—Sodium salicylate, in doses of 2 to 3 grams daily for several weeks, improves and cures certain cases of exophthalmic goitre.

2.—Quinine sulphate in doses of 1 to 2 grams daily is given alone or associated with ergot as a vaso motor constrictor.

3.—Anti thyroid medication, based on the theory of hyperthyroidism was first utilized by Ballet and Enriquez. The idea is as follows: neutralize the excess of thyroid secretion by the use of the blood of animals, whose thyroid had been removed. (The preparation usually employed is Hematoethyroidine).

According to Enriquez, the dose is as follows: 1 teaspoonful at each meal for one week, the first week; 2

teaspoonfuls at each meal the second week, and 3 teaspoonfuls the third week. After each three weeks of treatment, the patient is given one week of rest and in this manner the medication is kept up for three months. If after this period there is no improvement, the treatment can be discontinued.

The results of this treatment are as follows: 80 per cent. of the cases are improved, 10 per cent. are cured and 10 per cent. are unimproved or made worse (Sainton).

4.—Thyro Toxin serotherapy has been tried chiefly in America and has not been used very much in France. The idea results of the discovery of the cyto toxic serums and consists in the destruction of the thyroid cells. Its preparation and application has not yet been definitely established.

5.—Thyroid Organo Therapy seems paradoxical in cases of hyperthyroidism. In the majority of cases it makes the symptoms worse. It is, however, indicated in the cases where the disease evolutes towards myxedema, or in cases of Basedow's disease, which have not responded to anti thyroid medication, or in which symptoms of instability of the thyroid are present.

Large doses are always to be avoided and even small doses must be used very carefully.

6.—Various Other Forms of Organo Therapy.

Ovarian organo therapy is justified in the cases of Basedow's disease associated with ovarian insufficiency.

Thymus organo therapy, based on theoretical facts (hypertrophy of the thymus in Basedow's disease) has given such variable results that its indications are very obscure and doubtful.

Pituitary organo therapy advised by Renon, improves the tremor, the sweats, the tachycardia, the insomnia, and sometimes the exophthalmos and would seem to act as symptomatic medication. Hallion has shown experimentally that the extract of pituitary has a vaso constrictor action on the thyroid. Claude has observed that the extract of pituitary slows down the heart in cases of Basedow's disease and thinks that pituitary organo therapy has a favorable action on Basedow's disease.

III. TREATMENT WITH PHYSICAL AGENTS.

Tepid hydrotherapy sometimes gives excellent results.

Electricity has shown itself to be one of the best therapeutic measures. Faradisation has a vaso constrictor effect and decreases the secretion of the gland. Galvanization has a sedative and calming action. To-day both methods are used.

Radiotherapy was advocated first in America, then in France. It gives very variable results. Some are improved, others are not affected and we do not know why. It is usually the nervous and cardiac symptoms which are first improved.

IV. SYMTOMATIC TREATMENT.

The palpitations are attenuated by tincture of Strophanthus in rather large doses: 8 to 10 drops three times a day. Digitalis is indicated in cardiac insufficiency which complicates the disease.

The tremor can be improved by Belladonna and Jusquiam. Scopolamin is a less easily used drug and must be watched carefully.

The nervous disturbances are treated by sedative medications: bromides, valerian, antipyrin, aconite, etc.

The general condition is often improved by arsenic, phosphates, etc.

V. SURGICAL TREATMENT.

1.—Partial thyroidectomy, care being taken to leave untouched the parathyroids, to avoid tetany, and preserve enough of the gland to prevent myxedema is a commonly used method of treatment.

2.—Ligations of some of the blood vessels of the thyroid is considered by some to be the method of choice.

3.—Sympatheticectomy, advised by Jabouley, is practically never used any more.

THERAPEUTIC INDICATIONS.

All the methods of treatment given are not exclusive and can be associated with advantage.

1.—In classical exophthalmic goitre etiological treatment should be attempted: specific medication in goitre of syphilitic origin; salicylates if the patient has had acute articular rheumatism.

In the majority of cases all etiological indication is missing. The patients are first put on a regime of absolute mental and physical rest, then antithyroid medication is first tried. If the patient does not react to it, there is no use continuing the treatment too long. The electric treatment should next be tried, then radiotherapy associated with symptomatic medication or organo therapy, depending on the case.

If medical treatment fails or makes the condition worse then surgical treatment is indicated. This is counter-indicated in the cachectic cases and those with cardiac insufficiency, however. In the acute form with rapid evolution which usually resists all medical treatment, thyroidectomy should be resorted to.

2.—In goitres with symptoms of Basedow's disease, some are improved by antithyroid medication, others by thyroid organo therapy given carefully and in small doses.

If these medications do not give any results, then thyroidectomy is indicated. Radiotherapy is without any effect in these cases.

3.—The syndromes of Basedow's disease occurring at puberty, the menopause or during pregnancy, should be treated with ovarian organo therapy.

THYROID INSTABILITY.

Thyroid instability (Levi) is characterized by a disequilibrium of the functions of the thyroid. It results in the association, in various proportions, of signs of hypo and hyperthyroidism.

During the course of thyroid insufficiency, no matter what its degree may be, disturbances may be observed which are due to hyperfunction of the gland. Inversely, but not as frequently, in hyperthyroidism are seen symptoms associated to hypothyroidism. Some patients, for instance, show signs of hypothyroidism: constipation, alopecia, low body temperature and of hyperthyroidism: palpitations, insomnia, febril attacks, making one suspicious of a possible tuberculosis.

Thyroid instability has not only a theoretical interest but is very important practically and upon it must depend the treatment employed. Thyroid medication will not only improve the symptoms of hypothyroidism, but also those of hyperthyroidism; for these can be considered more or less as a reaction. There is, therefore, a thyroid disequilibrium.

Before administering thyroid to a patient with manifestation of chronic arthritis of thyroid origin, for instance, it is necessary to study the function of the gland. L. Levi advises to write on either side of a line the signs of hypo or hyperthyroidism found in each patient and to study also the reactions of the patient to menstruation, and emotions. Those in which hyperthyroidism predominates can be given very small doses of thyroid or 0.005 milligrams. Those in which the signs of hypothyroidism seem to predominate can be given larger doses: 0.05 to 0.10 milligrams. In those in which neither of the two predominate, intermediary doses are given: 0.025 milligrams.

According to L. Levi, the reactions to this medication regulate the doses of thyroid. It is easy to see how organo therapy, by using excessive doses, can overreach its objective and cause, in certain patients, the symptoms of hyperthyroidism. The symptoms of hyperthyroidism symmetrically opposed to hypothyroidism are schematized below to allow us to study the thyroid equilibrium in patients.

HYPOTHYROIDISM	HYPERTHYROIDISM
Dull Expression.	Exophthalmos, brilliant eyes.
Thyroid not appreciable in size.	Hypertrophied thyroid.
Fall of hair. Eyebrow sign.	Hypertrichosis, often cf the eyebrows.
Tendency to obesity.	Loss of weight.
Hypodermia.	Hyperdermia, waves of heat. Tachycardia.
Dry skin; transitory edema.	Moist skin, excessive secretion of sweat.
Sleepiness, apathy.	Insomnia, nervosity, irritability, etc.
Anorexia, constipation.	Tendency to diarrhea.

ACUTE THYROIDITIS, TUBERCULOSIS AND SYPHILIS OF THE THYROID.

INFLAMMATION OF THE HEALTHY THYROID is called thyroiditis; that of an altered gland, strumitis. The latter is the most frequent of the two.

Thyroiditis is observed most frequently in women between 20 and 40.

The causes are: traumatism, chilling, and particularly, infections; typhoid fever, pneumonia, septicæmia, scarlet fever, diphtheria, erysipelas, influenza, malaria, mumps and acute articular rheumatism. In rheumatism the thyroid is very often affected (H. Vincent).

The condition starts with a chill, headache, followed by a temperature and pains often very sharp radiating towards the ear, the neck, the shoulders and the back of the head. The patient usually takes the characteristic attitude of the head bent downwards with the chin in the hand. On examination a swelling of the thyroid is noticed together with some local temperature. Very quickly an intense dyspnea develops with attacks of choking, a paroxysmal cough, dysphagia and sometimes a complete aphonia. To these symptoms of compression are associated signs of hyperthyroidism; tachycardia, tremor, slight exophthalmos.

The evolution varies. Resolution is the rule in mumps and influenza. Suppuration occurs most frequently after pneumonia, typhoid fever and purpural sepsis. The skin then adheres to the gland, becomes red and edematous, but fluctuation rarely occurs and puncture may be negative due to the depth of the abscess. According to the nature of the causative factor pneumococcus, streptococcus or typhoid bacilli are found in the pus.

Gangrene rarely results, but when it does occur it usually is fatal.

The differential diagnosis is made between this condition and the tumefaction of the gland at puberty and during menstruation, which evolutes without fever; it also must be differentiated from adenitis and abscesses in the neighborhood of the gland and from neoplasms (sarcoma or carcinoma).

The treatment consists in the application of warm compresses and leeches. Tracheotomy may be indicated in the cases of dyspnea and suffocation. Surgical intervention has to be resorted to in suppurative or gangrenous thyroiditis.

* * * * *

TUBERCULOSIS OF THE THYROID is rare. For a long time is was believed that the thyroid tissue had a peculiar resistance to tubercle bacilli; as a matter of fact, like all vascular organs, it does not offer a favorable field to the development of the tubercle bacillus and the formation of tuberculous lesions.

1.—MILIARY TUBERCULOSIS.—Is the best known and most common type. It has no particular clinical interest and is usually found at autopsy as a secondary manifestation of tuberculosis.

2.—MASSIVE TUBERCULOSIS—of the thyroid is rare. It can be found in two different types of cases.

(*a*) Tuberculous goitre, which gives rise to a hard thyroid tumor, which causes respiratory disturbances by pressure and which sometimes simulates thyroid goitre, because of the rapidity of its growth, so much so that the extirpation of the gland may be necessary. This form causes caseation: the gland is studded with large solitary tubercles fresh or broken down.

(*b*) Cold abscess of the thyroid sometimes resembles a cystic goitre and may cause dysphagia, compress the larynx or the recurrent laryngeal nerve or the sympathetic. The patient can recover after incision and drainage.

3.—SCLEROUS TUBERCULOSIS OF THE THYROID—is found quite often in chronic tuberculosis (Roger and Garnier). The thyroid is atrophic, decreased in size and paler than normal. The connective tissue is considerably increased and is particularly abundant around the blood vessels and pénetrates into the gland in various directions, giving it a lobulated appearance resembling the thyroid of a child. The vesicle presents a variety of changes: in certain places the colloid is decreased, in others there seems to be hyperplasia of the cells. Endo and periarteritis is the rule, but there are no follicular lesions. Tubercle bacilli are not found; inoculation is negative. This thyroid sclerosis takes on the appearance of an ordinary inflammation.

Clinically sclerous tuberculosis of the thyroid gives the symptoms of a latent atrophic sclerosis. In very rare cases it may become hypertrophic and give rise to a hard tumor, developing rapidly and causing pain and respiratory disturbances. This is the so-called canceriform thyroiditis which simulates cancer. It may also cause a dysthyroiditis giving rise to abortive or typical symptoms of Basedow's disease. Laignel-Lavastine, Mantoux and Ramond have reported similar findings. The development of exophthalmic goitre on top of a tuberculosis of the gland are to-day well known. To the period of hyperthyroidism succeeds a period of hypothyroidism resulting in myxedema.

* * * * *

SYPHILIS OF THE THYROID is more common than is suspected.

In children, hereditary syphilitic sclerosis is possible in a certain number of cases of myxedema, and specific treatment is indicated in these cases as well as organo therapy.

Acquired syphilis is better known. During the secondary stage can be observed temporary congestions of the thyroid. Tertiary thyroiditis or gumma of the thyroid are found nearly always in women with a small goitre which has not been detected.

From a clinical point of view, syphilis of the thyroid causes either a myxedema or Basedow's disease or a goitre simulating a cancer.

Certain cases of conjugal or familial Basedow's disease are due to syphilis (Schulman). It, therefore, plays an important part in the etiology of exophthalmic goitre.

Mercurial or arsenical treatment can be employed indifferently. Iodides must be used with caution, although some of these cases will be greatly benefited by it.

Estimation of the Basal Metabolism can be used as an index of the activity of the Thyroid.

A Subnormal Basal Metabolism indicating Hypothyroidism, while an increase is evidence of overactivity of the gland.

CHAPTER II.

I. PATHOLOGY OF THE PARATHYROID GLANDS.

FUNCTIONS OF THE PARATHYROIDS

The parathyroid glands were discovered by Sabdstroem in 1880. They consist of two pairs of small glands, the size of a lentil, situated on either side of the thyroid. There are two superior parathyroids corresponding to the union of the upper and lower two thirds of each lobe of the thyroid (sometimes they are included in the thyroid itself) and two inferior parathyroids on the lateral surface of the gland, in the neighborhood of the inferior thyroid artery.

It has the structure of a gland of internal secretion although different from the thyroid. It consists of rows of glandular cells in intimate contact with the blood and lymphatic capillaries.

The product of their secretions is not yet well determined. All that we know is that the parathyroid cells contain a colloidal substance; iodine, glycogen, and various fatty substances, the exact part played by them not having been yet determined.

The parathyroid have certain peculiar physiological properties brought out at first by Gley and de Moussu and since then by other investigators.

Their destruction in animals results in three types of disorders: nervous, toxic and trophic.

1.—Nervous Disorders.—In the cat or the dog, in which all the parathyroids have been removed, certain phenomena occur two to three days after the operation. The animal begins to shake, has muscular tremors and contractures of the muscles of the feet, neck and from time to time generalized convulsions. The following days these phenomena become more frequent and more pronounced. It becomes impossible for the animal to stand up; it becomes cachectic and dies usually in from eight to ten days after the operation.

The total extirpation of the parathyroids, therefore, brings on fatal symptoms of tetany.

The experimental cases which do not follow this rule are explained by an incomplete removal or the existence of accessory glands and are proved by autopsy.

2.—TOXIC DISTURBANCES.—The animal whose parathyroid has been removed shows digestive disturbances (loss of appetite, dysphagia, intense thirst, abundant salivation, frequent vomiting), a rapid breathing, an increased heart rate; the excretion of urine is decreased, contains albumin and often sugar and diacetic acid. All these symptoms being signs of intoxication.

3.—TROPHIC DISTURBANCES.—They are observed in young animals who have only had a partial parathyroidectomy; arrest of development, loss of hair, cutaneous ulcerations, dental changes, etc.

Of all the disturbances, the first are the most important. The complete removal of these glands is incompatible with life. It determines symptoms of neuro muscular hyperexcitability (contractures and convulsions), comparable to those observed in man during tetany.

PARATHYROID SYNDROMES.

I. PARATHYROID INSUFFICIENCY AND TETANY.

Tetany is characterized by attacks of painful contractures localized to certain muscles (usually those of the extremities) and more rarely generalized.

This affection was first described by Dance then Tonnele and was considered for a long time to be of rheumatic origin or to be a variety of tetanus. It is following the experimental researches of Gley and Moussy in France, that certain clinicians, struck by the clinical resemblance between human tetany and the nervous phenomena observed in animals after the removal of the parathyroids, suggested that this disease might be the result of a disturbance of the function of the parathyroids.

THE SYNDROME OF TETANY.

Tetany must not be considered as an autonomous affection, but as a syndrome coming on under a variety of conditions and characterized on one side by contractures, on the other by a mechanical and electrical hyperexcitability of the nerves and muscles.

A. Contractures.—They are usually symmetrical and localized to the extremities. They are preceded by tingling and a sensation of falling asleep of the part which is somewhat painful. It affects the muscles of the hands and feet.

The hand can take one of two characteristic attitudes. It takes the shape of a cone due to the forced adduction of the thumb and all the other fingers pressed tightly against each other and in which the first phalynx is half flexed, while the other two are extended.

In the cases in which the hand is cupped, it resembles the position of an obstetrician making an examination. Sometimes the thumb is flexed in the palm and completely covered by the other fingers, also flexed. The contracture is sometimes so marked that the nails penetrate into the palm.

The foot gives a similar deformity and was described by Escherisch under the name of carpo-pedal spasm: the foot is in varus equinus; the planter surface is cupped and the toes are flexed.

These contractures are painful, involuntary and resist all attempts to overcome them. They occur after a simple movement, a change of position or without any apparent cause.

They can be brought out by Trousseau's sign: a compression of the arm at the level of the median nerve or above the clavicle at the height of the brachial plexus, will cause a tingling sensation followed by a contracture.

In some cases, these contractures become generalized and invade the upper limbs, the trunk. the legs, and the face. The hands become flexed at an acute angle to the wrists, the forearms on the arms; the latter are pressed tightly against the body. The legs are usually in extension. In the face the contractures are manifested by trismus, spasm of the eyelids and a sardonic smile. The lips are pushed forwards and simulate the mouth of a fish. The contracture may involve the muscles of the pharynx (dysphagia) and the larynx (spasm of the glottis), the vesicle sphincter (retention of urine), etc. Its generalization resembles the clinical picture of tetanus.

In certain abnormal cases the contracture stays localized to a group of muscles (muscles of one of the hands, for instance) or to one muscle (contracture of the thumb, spasm of the eyelids). The most important of these isolated contractures is that involving the muscles of the larynx. As has been shown by Bouchut, *Laryngospasm* is always a symptom of tetany. The spasm is then called phreno glottic. Laryngospasm is often seen in the tetany of infants.

B. HYPEREXCITABILITY OF THE NERVES AND MUSCLES.—This can be brought out by means of mechanical or electrical stimulations.

(*a*) The percussion of the facial nerve, done on the middle of a line between the external auditory canal and the labial commissure, causes a sudden contraction of the muscles of the commissure and those of the side of the nose, sometimes even one-half of the face. This is *Chvostek's* sign. Weiss's sign is analogous: percussion performed on the superior branch of the facial at the level of the external angle of the orbit causes a contraction of the frontal muscle and those of the eyelids.

(*b*) Investigation of the electrical excitability gives the following reactions:

1.—Galvanic hyperexcitability of the nerves and muscles and the possibility of obtaining muscular contractures on the closure of the Cathode with a current of loss of 1 milliampere. This is what has been termed Erb's sign.

2.—Hyperexcitability at the anodal opening current and predominence of the contraction on opening instead of a closing as normally occurs.

3.—Hyperexcitability at the Cathodal opening and the possibility of obtaining opening contractions with a current of less than five milliamperes.

These reactions are characteristic of tetany.

(*c*) Accessory Symptoms.—The reflexes are often exaggerated. Sensory disturbances are missing, except in very severe cases, which are accompanied by cramps and sharp stabbing pains. There are no sphincter disturbances outside of retention of urine from spasm of the sphincter. The temperature is usually normal except in very severe cases. The examination of the cerebro spinal fluid does not show any evidence of meningitis. In certain chronic cases vaso motor disturbances may occur: indurated edema of the back, of the hand, or of the foot, redness or cyanosis of the extremities, or of the face and during the attack trophic changes; falling out of the hairs, brittle nails, etc., as in experimental tetany.

COURSE—DURATION—ENDING.

In the mild cases the contractures stay localized to the ends of the upper extremities. They occur in attacks lasting anywhere from a few minutes to a few hours; rarely they may persist several days. A series of repeated attacks constitutes an attack of tetany; these attacks last on an average of about two weeks and end in recovery. Recurrences are, however, frequent.

In the moderately severe cases, the contractures are more pronounced. They are often accompanied by a slight fever, general malaise and vaso motor disturbances, erythema and edema. They can become generalized and involve the muscles of the trunk and the face, simulating tetanus.

In the severe cases, particularly in children, the contractures are accompanied by or alternate with tonic or clonic convulsions, followed by a coma and comparable to an epileptic attack.

In all those types of cases, death may occur by asphyxia, due to spasm of the glottis and contracture of the respiratory muscles (this is a real danger in infants), or by eclampsia during one of the epileptiform attacks. For this reason, the prognosis of tetany should always be guarded even in the mild cases.

CLINICAL MANIFESTATIONS OF TETANY.

I. SURGICAL TETANY OR POSTOPERATIVE TETANY.

This was first observed by Nathan Weiss in 1880 following the removal of a goitre. It was described by J. L. and A. Reverdin and by Kocher.

The disease manifests itself a few hours or a few days after intervention by a prickling sensation or stabbing pains in the limbs. Attacks of painful contractures occur, symmetrically localized to the fingers of the hand. This takes on the typical "obstetrical hand" appearance. These contractures may involve the feet or become generalized. The electric reaction shows a hyperexcitability and tetany. The mechanical hyperexcitability of the nerves is easily brought out by the Trousseau and Chvostek signs. The attacks, sometimes short, sometimes long, re-occur after a certain interval. They are often accompanied by fever, acceleration of the pulse, intense dyspnea, salivation and vomiting. All of which are toxic symptoms similar to those seen in experimental tetany.

Post operative tetany does not always manifest itself under this typical form. There are also convulsive forms (Fr. Hochwart) characterized by clonic or tonic convulsions and periods of quiescence.

This condition sometimes gets well spontaneously and completely. It can also become chronic, the attacks occurring at long intervals, but persisting for years. Kocher has observed it associated with myxedema. Some cases die, either as a result of spasm of the glottis or after a convulsion.

II. MEDICAL OR SPONTANEOUS TETANY.

This condition is seen:

1.—During the course of some cerebro spinal affection, especially in tuberculous meningitis, cerebro spinal meningitis, hemorrhages of the meninges, hydrocephalus, etc. In these cases tetany is only a nervous syndrome added to the primary infection.

2.—*Following gastro intestinal disorders.*—In children various gastro intestinal affections are often complicated by attacks of tetany. In adults, the most common cause is a gastric affection. Tetany is observed in the course of pyloric stenosis of ulcerative or neoplastic origin, following the vomiting, or when patients have used stomach lavage extensively. It may appear as localized contractures or generalized as epileptiform attacks, sometimes even it may take on a chronic appearance. Its prognosis is severe, particularly by reason of the lesions which bring it on.

3.—*In the course of infectious diseases.*—Typhoid fever, dysentery, cholera, measles, influenza, diphtheria, etc.; these can become complicated by tetany. This condition is usually mild; nearly always gets well and does not re-occur.

4.—*In various types of intoxications.*—Toxic tetany are very rare. They have been reported in delirium tremens, chloroform poisoning and uremia.

5.—*At various periods of the genital life of women.*—Tetany is occasionally met with at puberty. Rebaud considers this as a premonitory sign of menstruation. It disappears once menstruation has become regularly established. It is also reported during pregnancy. It ceases usually towards the sixth month, but is a rather serious complication, for the attacks are usually painful and last a long time. It may also occur after delivery in nursing mothers. It always gets well, but a recurrence is possible during each pregnancy and each lactation period. Finally Delpech and Dalche have seen it at the beginning of the menopause.

IDIOPATHIC TETANY.—It is most frequent during the first two years of life, but is sometimes observed in adults, usually in men between 16 and 25, nearly always in winter.

Tetany of infants occurs during a variety of diseases: measles, broncho pneumonia, athrepsia, congenital syphilis, etc. Two diseases play a preponderant part in the causation of this disease: rickets and gastro enteritis. But tetany may occur in infants without rickets, without any gastro intestinal disorders, and without any other disease.

DIAGNOSIS.

The diagnosis of the tetany syndrome is very simple. There is no disease simulating tetany, when the latter is characterized by localized contractures of the extremities occurring at intervals.

A differential diagnosis has only to be made in the chronic or generalized forms, in which the contractures last for a longer period of time. Tetanus is distinguished from it by the mode of onset of the contractures. The latter begins with the masseter muscles; trismus is an early sign, then comes dysphagia and then contractures of the back of the neck, trunk and extremities. In tetany trismus is missing or only appears late in the disease and the contractures begin with the upper limbs. The temperature is never as high as in tetanus: sweats are absent. Trousseau's sign, Chvostek's sign, and Erb's sign are missing in tetanus. The contractures caused by encephalo medullary organic lesions are permanent and associated with exaggeration of the reflexes and motor paralysis, the spasm affects all the limbs and not only their extremities.

Hysterical contractures have not the aspect of the evolution of tetany, and have none of the electrical or mechanical signs of the disease.

Lumbar puncture enables us to differentiate symptomatic tetany from meningeal affections.

PATHOGENESIS.

RELATION BETWEEN TETANY AND PARATHYROID INSUFFICIENCY.

We do not yet know the anatomical lesions causing tetany. This disease, which has been believed to be due to rheumatism, a central nervous affection, is at present considered as the expression of a parathyroid insufficiency.

Post operative tetany, described under the name of strumic tetany or acute post operative myxedema, is due, without a doubt, to destruction of the parathyroids in the course of partial or complete thyroidectomies.

Can medical tetany be considered as a manifestation of parathyroid insufficiency? Pineles has shown the clinical identity of the different types of tetany. In all the cases of tetany, be they post operative, infantile, gravid or idiopathic, the chief signs of the syndrome are present: contractures, convulsions, hyperexcitability of the nerves, electrical reactions. Furthermore, experimental tetany shows very similar symptoms. In animals in which the parathyroids have been removed, not only are the severe symptoms present but also the electrical hyperexcitability of the nerves.

(*a*) INFANTILE TETANY.—Many types of lesions of the parathyroids have been observed at autopsy of children having shown symptoms of tetany.

The most frequent are hemorrhages in the glands. Described by Erdheim, they have been studied by Yanase, Harvier, Strada, Auerbach, etc. They can be seen with the naked eye when the lesions are extensive. When they are discrete they can only be seen under the microscope. They are rarely found in all the glands; in the majority of cases only one or two glands are affected. The cause of these hemorrhages is unknown and their frequency very variable according to the writers.

In certain cases, generalized or localized glandular sclerosis has been noticed; in others, simple anomalies of the parathyroids, either in size or the number of the glands.

These various alterations, or anomalies, cannot be considered as the determining cause of tetany. They are also found in children who have never had any signs of tetany (Harvier, Auerbach, Strada). Furthermore, certain observers have not found any lesions of the parathyroids in children dying from tetany (Thiemisch, Ravenna, etc.).

(*b*) MATERNAL TETANY.—Vassale and his pupils have established in classical experiments the influence of pregnancy and lactation on the appearance of symptoms of tetany. Animals having had a well tolerated partial parathyroidectomy (a state of relative parathyroid insufficiency), presented in a subsequent pregnancy a severe or fatal tetany. Lactation had an analogous effect. A few autopsies of pregnant women dying from the eclamptic form of tetany have shown the presence of anomalies on lesions of the parathyroids (Pepere, Haberfeld). Finally, Vassale claims to have obtained excellent results by parathyroid organo therapy in certain cases of tetany.

These facts have allowed us to conclude that certain pregnant women have a latent or even relative parathyroid insufficiency, capable of becoming more pronounced during pregnancy (under the influence of some endogenous intoxication; hepatic insufficiency for instance), at time of delivery (due to extra muscular fatigue), and during lactation (by depletion of minerals). The remarkable likeness between experimental parathyroid eclampsia of the pregnant female and the spontaneous eclampsia of the pregnant woman have caused certain writers to believe, as does Vassale, that eclampsia is of parathyroid origin. This theory cannot be accepted without a certain reserve; it is very probable that all cases of eclampsia are not due to parathyroid insufficiency.

(*c*) GASTRO INTESTINAL TETANY.—It has not been possible to reproduce it experimentally. The anatomical reports on the condition of these glands in this type of tetany are rare and not very convincing. It is possible, furthermore, that the action of the toxic substances on the nervous system, resulting from pyloric stenosis or other intestinal affections, are sufficient to explain the tetany manifestations without it being necessary to invoke the action of the parathyroids.

(*d*) The action of the parathyroids in the other types of cases is doubtful and questionable. Histological examination in tetany of infectious origin in adults is missing. In a tuberculous woman, developing tetany, Carnot and Delion found a tuberculous caseation of one of the glands, but were unable to find some of the other parathyroids. Winternitz in 1905 published a similar report.

When all is said, only the post operative forms of tetany can be considered unquestionably to be due to parathyroid insufficiency. Medical tetany, because of its similarity to surgical tetany, has a possible parathyroid etiology, but the anatomical reports and the results of organo therapy do not allow us yet to confirm this possibility in all the cases observed.

How does parathyroid insufficiency determine tetany? Two theories are suggested:

1.—CALCIUM THEORY.—The observations of Loeb, who in 1900 showed the relationship between neuro muscular hyperexcitability with a decrease in the calcium salts, then the experimental work of Frouin, Parhon and Urechie, showing that the absorption of calcium chloride after parathyroidectomy, prevented the appearance of the nervous symptoms, have led us to believe that parathyroid insufficiency caused an excessive secretion of calcium. The parathyroid glands regulate the metabolism of calcium, just as the pancreas regulates that of glucose. They have an inhibitory action on the excretion of calcium. Tetany is a calcium diabetes.

2.—TOXIC THEORY.—According to Pfeiffer and Mayer, Berkeley and Beebe the accidents of tetany are of a toxic nature. They are produced by endogenous poisons normally destroyed by the glands or neutralized by their secretions. Among these poisons, the most important would be guanidine, one of the by-products of nitrogen metabolism (N. Paton and Findlay).

TREATMENT.

Post operative tetany necessitates a preventative and curative therapy.

To avoid any accident the surgeons have devised various manners of performing thyroidectomy so as to avoid the parathyroids. The main idea consists in avoiding any manipulation in the neighborhood of the glands. When tetany does occur after removal of the thyroid, two types of medication can be given:

1.—Symptomatic Medication.—Anti spasmotic (chloral and bromides), calcium medication has given good results in the shape of the lactate or the chlorides (Mayo, Grath, Meltzer). The daily dose is from 2 to 6 grams.

2.—Specific Medication.—This includes organo therapy and parathyroid grafts.

The ingestion of fresh glands, or the injection of parathyroid extracts have caused the various phenomena to disappear in the patients of Callum, Pool, Halsted, etc. We must, however, add that the majority of these cases only had had a partial removal of the parathyroids. The action of organo therapy is temporary and by preventing the various symptoms developing, allows a compensatory hypertrophy of the remaining glands until these are capable of carrying on their function.

Parathyroid grafts have the advantage, when successful, of assuring permanently the glandular function. It unfortunately has many technical difficulties. However, when during the course of a surgical operation, it is found that one or more of the parathyroids has been removed, auto graft should be done at once in the parenchyma of the thyroid, where it has a good chance to succeed. In the majority of cases, however, it is only performed after the appearance of the symptoms of tetany; auto graft is then impossible and specimens must be obtained from other individuals. As animal grafts do not succeed, they have to be obtained from individuals who have died in an accident or to remove one of the parathyroids in a patient who is operated upon for goitre. Human graft has been successful in the hands of Pool, Czerny, Kocher, etc.

3.—Symptomatic medical tetany disappears with their cause and their treatment is related to the primary disease: diphtheria antitoxin in diphtheria, tetanus antitoxin in tetanus, lumbar puncture in meningeal affections, etc.

4.—Idiopathic tetany is treated by tepid baths, sedatives: bromides, chloral and calcium chloride.

Parathyroid organo therapy is given under the form of a fluid extract, given in doses of from 60 to 100 drops daily, or the dried extract of ox or horse gland, given in doses of from 5 to 20 milligrams daily. Marinesco, Vassale, Zanfrognini, etc., have obtained good results with this in infantile and gravid tetany. The failures are, however more numerous than the successes.

II. POSSIBLE PARATHYROID SYNDROMES.

So called essential epilepsy has been suggested as being of possible parathyroid etiology. Vassale, Parhon and Golstein have obtained favorable results in epilepsy with parathyroid medication. Claude, Schmiergeld and Schmorl have found at autopsies of epileptics numerous appreciable lesions of the parathyroids. Other glands, however, such as, the thyroid for instance, are affected just as frequently and the parathyroid theory of epilepsy is still to be proved.

Parkinson's disease was considered by Lundborg in 1904 as a chronic syndrome of parathyroid insufficiency. Parathyroid organo therapy when it has been tried has however given very contradictory results and, furthermore, the anatomical study of these glands in Parkinson's disease has never shown constant lesions. J. Gauthier who has recently taken up this disease, as regards to its relation to endocrines, believes it to be due to a thyroid-parathyroid insufficiency. All these facts are hypothetical and very questionable.

III. SUDDEN DEATH IN CHILDREN AND LESIONS OF THE PARATHYROIDS.

The part played by the parathyroids in the pathogenesis of sudden death in children is still to be determined. We have, however, a few cases which help us to interpret it. One of these was reported by Triboulet, Ribadeau-Dumas and Harvier and occurred in a congenital syphilitic, one month old infant. Autopsy showed a variety of lesions of the blood organs: adrenals, pituitary, thyroid and parathyroids. The latter showed severe hemorrhages and contained trepenoma. Grosser and Berke found on post mortem examination of three infants, who died very suddenly, hemorrhages localized to all the parathyroids. It is, therefore, important in all autopsies of children dying very suddenly to examine parathyroid glands, as well as the other endocrines.

CHAPTER III.

I. PATHOLOGY OF THE THYMUS.

FUNCTIONS OF THE THYMUS.

The thymus in man consists of a cervical part, made up of two diverging cones, which are attached to the thyroid by fibrous tissue and are closely approximated to the brachio cephalic and jugular venous trunks and a mediastinal part located between the chondro-sternal portion of the thoracic cage in front, and the pericardium and the large vessels at the base of the heart and the right ventricle in the back.

In the child, the thymus is a reddish gland, of soft consistency, plastic, which moulds itself to the blood vessels, insinuates itself between them and comes in contact with the anterior surface of the trachea. It is not a definitely demarcated organ: at a certain time of life it atrophies, but does not, however, disappear completely. There is a fatty change in the gland, but glandular lobules still persist and in certain pathological conditions can regenerate.

The time at which the thymus reaches its greatest period of development and the time at which it begins to atrophy is still unsettled. The French investigators give as the weight of the thymus the following figures: at birth 3 to 5 grams (Hutinel and Tixier, Cruchet); at one year from 5 to 8 grams (Marfan); between 3 and 4 years from 7 to 9 grams. According to some the regression begins at the age of two, for others at four.

Hammer, and then Sury, by studying the weight of the thymus in individuals dying in accidents give very different figures: at birth the thymus weighs 13 grams; from 1 to 5 years of age about 22 grams; from 6 to 10 years about 26 grams and from 11 to 15, 37 grams on the average. According to these writers, the weights usually given are erroneous, due to the fact that various illnesses influence the weight of the gland. It quite rapidly becomes atrophic when the nutrition becomes deficient, in various types of infantile cachexia, and during acute infections: measles, scarlet fever, diphtheria, etc. The histological investigations of Roger and Ghika, of Lucien and Parisot have shown the frequency of thymus lesions in the young, indicating a marked degeneration of the gland. Next to the physiological evolution and parallel to it there exists a pathological evolution, which may affect the first.

In spite of all this, it seems to be generally admitted that the normal involution of the thymus does not begin until between the 10th and 15th year. Until puberty it grows regularly and then gradually regresses.

The thymus is at the same time a lymphoid, blood forming and internal secretion organ, for its removal in animals causes a variety of symptoms. The functions of the thymus which up to the present time have been well established are:

1.—ACTION ON GROWTH AND DEVELOPMENT OF THE SKELETON.—This has been shown by the experiments of Tarulli, Lo Menace, Basch, Lucien, Parisot, and U. Seli. Animals in which the thymus was removed show a delay in growth, a reduction in height and volume of the bones. According to Basch, the bones are more flexible and transparent than normal, due to a decrease in the calcium content. According to Lucien, Parisot and U. Seli, however, the calcium content remains normal and the resistance of the bones is not decreased. The earlier the animal is operated upon, the more marked the delay in growth. There is practically no change if the animal has reached its normal growth.

2.—Action on General Nutrition.—It is parallel to the preceding. After the removal of the thymus the weight curve decreases slowly in comparison to that of controls.

3.—Action of the Genital Glands.—The development of the ovary and testicle shows a marked delay after the removal of this gland. It seems as if there was a balance between the thymus and the genital organs and that the thymic involution begins at puberty at the time when the genital glands become active.[1] In the castrated male animals, the thymus atrophies much later than in controls (Cazolari).

4.—Action on the Blood Pressure.—Extracts of thymus taken from children or animals, injected intravenously cause a marked drop in the arterial pressure. This hypotensive action which also belongs to the extract of lymph glands, should not be looked on as the result of an internal secretion. In athrepsia, atrophy of the gland goes hand in hand with a decrease with its hypotensive properties (Lucien and Parisot).

When all is said, there probably is an internal secretion to the thymus, although we do not know of any specific substance in this gland; its constituents have not the appearance of a glandular epithelium, and the clinical suppression of the thymus does not cause a clinical syndrome comparable to the removal of the thyroid or the parathyroids.

THYMIC SYNDROMES

A. SYNDROMES OF THYMIC HYPERPLASIA.

The thymus is affected by acute or chronic affections (Roger and Ghika), but this reaction is purely histological. There are no clinical evidences of this

---

[1] Clinically the administration of thymus extract controls menorrhagia and metrorrhagia when due to functional hyper ovarian stimulation. In fact in cases of uterine bleeding of obscure origin thymus can be used as a therapeutic test.

In certain cases, hyperplasia of the thymus causes in young infants a very definite clinical syndrome commonly known under the name of enlargement of the thymus.

I. HYPERTROPHY OF THE THYMUS.

SYMPTOMS.

We will simply give the chief clinical findings.

In its usual form, it is characterized by respiratory and circulatory disturbances. The child has a loud and harsh inspiration and expiration; inspiration is, however, the louder of the two. This is associated with a marked drawing in. Attacks of suffocation occur which may last from a few seconds to quite a long period of time, and in which asphyxia and even death may occur. During these attacks, and also during the interval, the veins of the neck are prominent and the face is cyanotic, showing a disturbance in circulation. These attacks come on without any apparent reason or after a fit of temper or tears. The drawing in of inspiration, the cyanosis and the inspiratory and expiratory râles are exaggerated in certain positions; such as, in the hyperextension of the head for instance.

In other types of cases, the respiratory disturbances are not continuous. Periods of suffocation do occur, but in between respiration is normal.

Percussion of the manubrium and the radioscopic examination of the mediastinum allow us to find the cause of these respiratory difficulties in a hypertrophy of the thymus and differentiate this condition from analogous conditions of childhood.

In these cases the therapeutic indications may be Radiotherapy or partial removal of the thymus.

ETIOLOGY.

We do not know the causes of thymus hypertrophy. Marfan considers it as one of the forms of proliferation of the hemo lymphatic organs, due to infections or auto intoxication of infancy: syphilis and tuberculosis would seem to be the most important. The disease occurs often in association with rickets and enlargement of the spleen. Very often however, it is an isolated affection observed among apparently healthy children without any evidence of rickets or any other disease.

PATHOLOGICAL ANATOMY.

The weight of the thymus varies between 25 and 200 grams. The gland may keep its normal aspect; that is, simply enlarged. Sometimes it is red, congested, more resistant than normal and filled with fluid when incised. The histological examination then reveals the reactions to an infection of the thymus: lymphocytes replaced by mononuclears, polynuclears, myeclocytes, corpuscles of Hassal showing recent degenerations. The blood vessels are dilated, filled with red cells, the tissues sometimes contain hemorrhagic foci visible to the naked eye.

PATHOGENESIS.

How does a hypertrophy of the thymus cause respiratory difficulties? The trachea is the first organ to which attention is drawn. Its compression has shown during life by means of the tracheoscope: Jackson noticed its flattening at the superior level of the thorax. The operative observations in the course of thymedectomy and numerous autopsies have shown the trachea bent, flattened and crushed. To see these changes at autopsy it is necessary to take certain precautions, as due to its elasticity, the trachea will take up its normal position again, as soon as the thorax is opened. It is necessary to remove, as one mass, the thymus, the trachea and the large vessels and fix this mass in formaldehyde before studying the relationship of the different organs or, again, as advised by Marfan perform the autopsy in this region by following the operative technique without opening the thoracic cage. The capsule of the thymus being incised, pressure is exerted on the lateral sides of the thorax and this will cause the thymus to rise above the manubrium. It then becomes easy to determine if it is exerting any pressure on the trachea. The question has come up as to how such a soft organ as the thymus could cause any effect on such a resistant organ as the trachea. This is due to the fact that the gland acts less by its weight than by its volume and this varies according to the circulatory conditions. The trachea can also be compressed indirectly by the intermediary of the large vessels at the base of the heart. In an observation of Barbier the right trachio cephalic arterial trunk deviated by the thymus had compressed and formed a groove in the trachea, which it compresses directly.

The large veins at the base of the neck can also be more and more flattened out by a hypertrophic thymus. Although this compression is hard to determine at autopsy it is very probable and such a theory alone could explain the cyanosis increased by extension of the head.

The compression of certain nerves (vagus, recurrent laryngeal, thymic nerve, etc.) is probable. Cruchet even believes that this nerve compression is more liable to occur than that of the trachea, but there is no definite fact to prove this.

The mechanical theory of compression is sufficient to explain the symptoms of hypertrophy of the thymus as it usually occurs, which is characterized by continuous respiratory disturbances. The intermittent type is due without a doubt to congestion of the hypertrophic thymus, usually fairly well tolerated.

At the autopsy of certain children dying of thymic accidents, the gland has been found very slightly enlarged or not at all. In these cases, these accidents can be explained by an abnormal conformation of the superior opening of the thorax. The latter is bounded by a sterno-costal-vertebral belt. The space between the sternal manubrium and the 7th cervical is the critical space described by Grawitz and has a diameter in the new born which varies between 2 and 2:5 cm. Following a congenital malformation or a rachitic deformity of the ribs, this diameter may be narrower than normal. Under the influence of many factors, notably the extension of the head, the thymus, which is a mobile organ and follows the movements of respiration, becomes strangulated in this body space. This strangulation causes a congestion of the gland; it increases in size, compresses the large vessels and the trachea and results in respiratory disturbances.

II. SUDDEN DEATH OF THYMIC ORIGIN.

Next to the thymic symptoms due to asphyxia, which are particular to childhood, there are certain types of syncope which are to be found at all ages.

1.—In the New Born or Young Infant.—These occur at night without any premonitory symptoms. The infant goes to sleep at night and the next morning is found dead in bed. It is usually believed that the child has been smothered under the bed clothes or that a crime has been committed. Autopsy reveals a hypertrophy of the thymus. Sometimes these sudden deaths do not occur in isolated cases. Griffith recently reported a family in which 7 out of 8 children died suddenly.

2.—In Older Children or in Adults.—Sudden death of thymic origin sometimes also occurs, the patient being in splendid health or following some shock or some trivial incident; such as, a cold bath, etc. Whether in a child or an adult, the phenomenon occurs very rapidly and the syncope is very different from the mechanical asphyxia. Furthermore, at autopsy, the hypertrophied thymus does not seem to have compressed any of the surrounding organs.

3.—SUDDEN DEATH DURING ANESTHESIA.—It occurs under similar conditions. The patient, usually young in years, is anesthetized for an operation. In the middle or at the end of the operation, sometimes even a few hours afterwards, occurs a cardiac syncope without any warning. The face becomes pale, the pupils dilate, the heart stops, while the lungs keep on functioning. All means employed to revive the patient, such as, artificial respiration, direct massage of the heart, etc., are of no avail. The condition is always fatal. It is independent of the choice of anesthetic, for it is observed just as well with ether, as with chloroform, or ethyl chloride. It is also independent of the doses used as it sometimes occurs after the administration of only a few drops, the patients sometimes having been anesthetized previously without any untoward effects.

On autopsy, the thymus is found usually enlarged weighing 30 to 40 grams, hypertrophied or at least in which involution has not occurred.[1] (1) Sometimes also the spleen is swollen, the superficial and deep glands are increased in size as well as Peyers patches and the closed follicles of the intestines.

---

[1] Lucien and Parisot have very rightly drawn attention to the fact that a certain number of observations of sudden death due to hypertrophy of the thymus gave a weight for the gland which varied from 10 to 22 grams in children and 20 to 50 grams in young adults. In these cases the hypertrophy is not real and may not be the cause of the death. In order to be able to testify that there is a hypertrophy of the thymus, it is necessary that the weight of the organ be notably higher than that for the average for the age of the individual. This is important from a medico-legal point of view.

PATHOGENESIS.

Several theories have been brought out to explain the sudden death.

(*a*) According to Paltauf, the patients, the children in particular, have a peculiar appearance. They are fat and anemic, having small genital organs. The tonsils, the glands of the neck and axilla are swollen; the spleen is increased in size. The cardio-aortic system shows aplasia. The examination of the blood shows an appreciable lymphocytosis. In other words, these subjects show a status lymphaticus characterized by hyperplasia of the lymphoid tissue and hypoplasia of the cardio arterial system. This diatheses shows a peculiar vulnerability of the heart as evidenced by the vagotonia; the sudden accidents are the result of an inhibition of the heart by the rupture of the equilibrium between the tonus of the vagus and of the sympathetic.

(*b*) According to Svehla, the syncope is due to a toxemia. The thymus secretes an abnormal secretion (quantity or quality) which results in a hyperexcitability of the cardiac nerve centers. All stimuli, which normally would be without effect, in healthy individuals, will cause in these susceptible cases a fatal syncope. This theory would help to explain the cases in which the gland is not hypertrophied.

(*c*) Others finally believe that the fatal syncope is due to a pressure on the vagus or the phrenic or even the right inferior cardiac nerves.

None of these theories, however, ingenious they may be, have ever been demonstrated and the pathogenesis of sudden thymic death is still hypothetical.

III. HYPERTROPHY OF THE THYMUS IN DISEASES OF THE ENDOCRINES.

Hypertrophy of the thymus has been noticed in simple goitre, in myxedema, in acromegalia, but so far, there is no proof of any relationship with these affections and enlargement of the thymus.

It is particularly in exophthalmic goitre that the frequency of hypertrophy of the thymus has been noticed. Capelle in 1908, Malti in 1912, have given operative statistics which seem to show that 75% of exophthalmic goitre cases which die during operation have an enlarged thymus. For this reason, the majority of German and American surgeons consider the action of this gland very important in Basedow's disease and advise removal of part of the thymus in the treatment of this condition.

This conception is not accepted in France. Lucien and Parisot have noted in Basedow's disease (as is also the cases in acromegalia) that the persistence of the thymus is not constant. When it does exist, the weight of the gland is very variable. Experimentally, these writers were not able to establish any relationship with it and the thyroid or the pituitary, for thymedectomy does not result in any anatomical regression or change of function of the thyroid. The presence of the gland should be considered as an abnormal persistence. Lenorman who has investigated this condition rather carefully has shown that in exophthalmic goitre the removal of the thymus has no more effect than the administration of extract of thymus.

These facts should, however, stimulate the clinician to look for signs of thymic enlargement in Basedow's disease and when found to have it treated by radiotherapy. If during the course of an operation on the thyroid, an unsuspected enlarged thymus is discovered, it is indicated to remove it at the time of the partial thyroidectomy.

B. SYMPTOMS OF APLASIA OR HYPOPLASIA OF THE THYMUS. CONGENITAL THYMIC IDIOCY.

On post mortem examination of many deficient children, no cerebral lesions are found. The thyroid is normal, but the thymus is absent. At Bicetre from 1890 to 1903 out of 408 autopsies of non-myxedematous mentally deficient children, the thymus was only present in 104 cases (L. Morel).

The recent investigations of Carre, and Lampus have also noted an aplasia of the thymus very marked in idiots with bony deformities resembling rickets or osteomalacia.

It is possible that thymic idiocy can be classified next to thyroid idiocy by aplasia of the gland.

The experiments of Basch, Klose, Vogt, L. Morel and Lampus have shown that young dogs, several months after thymedectomy, without bony deformities, developed psychic changes characterized by sleepiness, total apathy and the animals died usually in a year or a little more from cachexia. The experimental syndrome after removal of the thymus shows therefore, certain cases of idiocy, accompanied with disturbances, not involving the bones which are very similar.

CHAPTER IV.

PATHOLOGY OF THE ADRENALS.

FUNCTION OF THE SUPRARENAL GLANDS.

The suprarenal glands are made up of a cortical and a medullary part, which seem to be distinct from each other, both in their physiological and pathogenic functions.

To the two adrenal glands are connected a whole group of formations, the structure of which resembles either the structure of the medulla or of the cortex and which constitute all together a suprarenal system, scattered along the greater sympathetic.

Since the first experiments of Brown-Sequard (1856) a number of physiologists have shown the vital importance of this organ.

While the removal of one capsule is without any appreciable effect, that of both glands will cause the following symptoms: the animal becomes listless, stays stationary, moves his legs with difficulty, shows an extreme fatigue and muscular weakness. This asthenia progresses, while at the same time respiration becomes slower and the heart beat becomes weaker, while the blood pressure falls. Vomiting occurs, accompanied by diarrhea, the animal loses weight and dies very shortly from convulsions or syncope.

A double removal of the adrenals causes in animals:

1.—Muscular disturbances: decrease in muscular work.

2.—Cardio vascular disturbances: decrease in blood pressure and acceleration of the heart.

3.—Digestive disturbances: anorexia, vomiting, diarrhea.

4.—General disturbances: hypothermia, loss of weight, and particularly loss of muscular tissue.

5.—An increase in the toxicity of the exudates and transudates.

6.—Accessorily various lesions of the central nervous system and the greater sympathetic.

If the removal of the adrenals has been incomplete and a small piece of glandular tissue remains (1/11 of the total weight), the suprarenal functions remain intact and the animal survives (Langlois).

* * * * *

The physiological study of the action of the extracts of the suprarenals complete the knowledge of the function of the adrenals. In 1895 Oliver and Schafer established the fact that the injection intravenously of the extract of adrenals caused an increase of the blood pressure and Langlois showed that the same results could be obtained by injecting blood coming from the adrenal veins. This action was due primarily to an active principle secreted by the glands, suprarenalin, discovered by Takamine in 1901.

Suprarenalin acts not only on the blood pressure, but also on the heart and the blood vessels. It increases the strength of the cardiac muscle by the intermediary of the sympathetic whose normal stimulant it is; it interferes with the inhibitive action of the vagus on the myocardium (Roger). At the level of the blood vessels, it causes a marked vaso constriction and a corresponding increase in blood pressure. In the pulmonary circulation it will cause in toxic doses acute edema of the lung.

Suprarenalin is also a poison of the blood vessels and in repeated doses will cause atheromata in animals (Josue).

It also influences the regulation of glucose: in dogs and in rabbits it will cause a glycosuria when injected subcutaneously (Blum).

All these facts have an application in human pathology.

The adrenals have two main functions:

1.—AN ANTITOXIC ACTION.—The adrenal secretion has a specific neutralizing effect on certain poisons, the most important of which are those resulting from muscular effort and fatigue. When the glands are destroyed or deficient, the most marked symptoms are muscular fatigue and listlessness, which is very characteristic. Asthenia, which we will study in man is one of the most important symptoms of adrenal insufficiency. These glands also neutralize certain endogenous poisons. They become hypertrophic during pregnancy (Guiesse) for pregnancy can be considered as a state of auto intoxication.[1]

This antitoxic action can exert itself also, to a certain extent, on exogenous poisons; this, however, has not been definitely proved experimentally.

This antitoxic action belongs to the cells of the cortex, which are rich in lipoids, particularly cholesterin.

2.—AN ANGIOTONIC ACTION.—This normally presides to the maintenance of the blood pressure and is obtained from the medullary cells or chromaffin cells, which secrete suprarenalin.

* * * * *

The various morbid factors act on these types of cells causing a disturbance of their function and resulting in two great adrenal pathological syndromes:

1.—A syndrome of adrenal insufficiency.

2.—A syndrome of hyperfunction of the adrenals.

---

[1] Obstetricians should note this. The administration of corpus luteum in the vomiting of pregnancy has not had notably good results.

CHAPTER V.

SYNDROMES OF ADRENAL INSUFFICIENCY.

Our conception of adrenal insufficiency only goes back to 1855. Addison at this time described a disease, which has since been given his name, characterized by a progressive asthenia, and accompanied by circulatory disturbances, pains and pigmentations of the skin, giving it a particularly bronzed appearance. He believed that this bronzed affection was due to some alteration of the adrenals.

Soon after a number of observers published cases in which lesions of the adrenals had occurred without any pigmentation. Dieulafoy and his pupil Bressy have published under the name of "abortive forms of Addison's disease" clinical observations characterized by the signs of Addison's disease without pigmentation.

Sergent and Bernard, following the investigations of Brown-Sequard, continued by Abelous and Langlois, showed that the disease described by Addison was in reality a complex syndrome in which two types of symptoms could be made out; those resulting from an adrenal insufficiency (among which asthenia and circulatory disturbances) and symptoms resulting from an irritation of the sympathico suprarenal nervous system, among which pigmentation was the most characteristic.

They described adrenal insufficiency as: the expression of the decrease or the suppression of adrenal functions and separated it from the syndrome of Addison, characterized by pigmentation. They considered the "bronzed disease" described by Addison as an association of the syndrome of adrenal insufficiency with that of a sympathetic affection.

* * * * *

I. ADRENAL INSUFFICIENCY.

CLINICAL STUDY.

This is characterized by three cardinal symptoms: asthenia, arterial hypotension and the adrenal white line.

1.—Asthenia.—According to the etiological factor, the asthenia is very progressive or very abrupt. When progressive, it is characterized by a physical and intellectual lassitude which can only be satisfied by rest and which the patient cannot overcome by any effort of the will. This lassitude soon changes to prostration and complete apathy. The slightest effort causes such a sensation of fatigue and is so painful, that the patient stays still in bed in a semi sleep. He avoids speaking and only answers with difficulty to the questions asked him; does not want to eat so as to avoid moving. This asthenia is not a subjective sensation; it is shown objectively with the dynamometer by a marked decrease in the muscular strength in spite of the fact that the patient does not show any paralytic symptoms.

2.—Arterial Hypotension.—It indicates the failure of the angiotonic action. This drop is manifested both in the systolic and diastolic pressure. The pressure may drop to 90 or 80 cr even below. It is very unstable, varies from one minute to the other and reaches its lowest level after fatigue or an effort.

3.—The Adrenal White Line (Sergent).—The so-called white line of Sergent is in a way the opposite of the red line (tâche) of meningitis. To bring it out all that is necessary is to stroke the skin of the abdomen with a blunt object or the soft part of the finger, without scratching or exerting too much pressure. Very shortly will appear, on the course followed on the skin, a white line, rather broad which increases gradually, then stays stationary for a certain length of time.

The diagnostic value of this sign has been contested by L. Bernard and by Massary, who considers it as a vaso motor phenomenon, which may appear in a variety of conditions. It is possible that when found alone the white line is simply a nervous disturbance, showing itself by a vaso motor instability. Furthermore, the white line does not exist in all cases of hypotension. According to Castaigne it shows a vascular collapse, a decrease of the angiotonic function, while hypotension indicates insufficiency of the cardio tonic function. When this white line is found associated with hypotension and a certain degree of asthenia, then it has a real diagnostic value.

To these three main diagnostic signs are added other clinical manifestations:

1.—Circulatory Changes.—Closely related to hypotension. Some are subjective; the patient complains of palpitations and precordial pain; the slightest effort may be followed by syncope. The others are objective; the pulse is small, often rapid, weak, easily compressed and very unstable; the heart is accelerated. The slightest fatigue is susceptible of causing an attack of tachycardia with arythmia.

2.—Digestive Disturbances.—They are nearly always constant. Anorexia is the rule, at first in the morning and resembles that of alcoholics. Later it may come on at any time after the ingestion of food. Sometimes it is incoercible, particularly in children, and prevents all ingestion of food. Constipation is the rule in the slowly evoluting cases; in the acute forms there is a diarrhea. It is associated with abdominal pains and together with vomiting simulates poisoning.

3.—The Pains.—These are usually localized either in the lumbar region, or the epigastrium, or the hypochondria. In the latter cases they are usually limited to a special spot corresponding to the extremity of the 12th rib (Martineau's point). Sometimes they radiate to the thorax and shoulders. Whether continuous or intermittent, they are generally exaggerated by motion and are sometimes so severe that they cause the patients to cry out. In certain acute cases of adrenal insufficiency, the pains are generalized and the patient complains of stabbing pains in the limbs simulating the muscular cramps of cholera.

4.—General Disturbances.—These disturbances of toxic origin are very variable. They consist of a psychic asthenia characterized by a half conscious state, or prostration. Sometimes they are quiet, at others they have nightmares, and even delirium. Later on coma sets in.

Among these nervous phenomena, some have a sudden onset: they are manifested by an encephalitis accompanied by convulsions, cerebral stimulation, delirium and are ended by a deep prostration which terminates in death.

5.—General Signs.—The temperature is normal or subnormal and the patients complain of feeling chilly. The anemia is often quite marked (decrease in both red cells and hemoglobin) and is associated with buzzing of the ears and vertigo.

The urines are decreased in quantities, sometimes contain albumen and are very toxic. Finally, loss of weight and emaciation, particularly of the muscles, is the rule.

CLINICAL FORMS.

The signs of suprarenal insufficiency can be divided into two main groups: chronic and acute suprarenal insufficiency. Between these two types can be found many intermediary forms.

A. SLOW SUPRARENAL INSUFFICIENCY.

It is noticed in the course of chronic affections of the adrenals, which cause a slow decrease in the functions of the glands. The most definite type is Addison's disease, which we will describe very shortly, but which must be given a place here. If this disease is a mixed syndrome of adrenal insufficiency associated with an irritation of the sympathetic, certain types which have been described as abortive cases of Addison's disease, because of the lack of pigmentation, are really *pure* cases of adrenal insufficiency slowly evoluting and which only differ from the acute type by their duration, which is anywhere from 1 to 3 years.

B. ACUTE SUPRARENAL INSUFFICIENCY (syndrome of Claude Bernard.)

It corresponds to a sudden decrease or suppression of the adrenal functions.

While slow adrenal insufficiency is due to a decrease, ordinarily progressive, of the adrenal functions, so that the symptoms take a long time to develop, acute insufficiency is due to the sudden suppression of the glandular functions following the destruction of the gland. It gives rise to severe symptoms which are rapidly fatal. It occurs sometimes in individuals apparently in good health, or in the course of an infectious disease, or again following a slowly evoluting case of which it will be the ending.

The syndrome manifests itself under three different forms:

(*A*) Abdominal Type. (*a*) The symptoms develop suddenly with abdominal pains which are severe, diffuse and accompanied by incoercible vomiting, and even severe diarrhea. These gastro intestinal symptoms are followed by cramps. The patient is covered with a cold perspiration and the extremities are cold; the pulse is small, rapid and feeble. The temperature is subnormal and the patient dies in a few days, or sometimes immediately, following some slight movement in bed of cardiac failure. These cardio intestinal types which are the result of an acute adrenal insufficiency, simulate poisoning or cholera.

(*b*) In some cases the symptoms consist in vomiting with severe constipation and abdominal pain. The abdomen is hyperesthetic and distended with gas. Often an appendicitis or peritonitis is suspected; whence the name of pseudo peritonitis or syndrome of Ebstein. The patients die shortly afterwards.

(*B*) NERVOUS TYPE. Adrenal encephalopathy of Sergent.

In certain cases adrenal insufficiency takes on a nervous symptomatology:

Comatous phenomena, which are rapidly fatal and simulate apoplexy.

Convulsive phenomena or myoclonic movements.

Delirium (Laignel-Lavastine).

Pseudo meningitis (Sergent). In these cases the encephalitis, the rigidity of the neck, the cutaneous hyperesthesia, the photophobia, the opisthotonos, the delirium, associated with vomiting and constipation, give the picture of meningitis. Kernig's sign, is however, missing and the spinal fluid remains normal.

(*C*) SUDDEN DEATH.—All the preceding types of cases can end by sudden death. It may happen any time during the evolution of a slow or acute adrenal insufficiency. It is sometimes the only manifestation of this insufficiency and really is an acute form of adrenal insufficiency. Death is often instantaneous, following some simple movement. It can sometimes be preceded by an extreme dyspnea, the duration of which is, however, of more than a few minutes, with pallor of the face, precordial pain, or an epiliptiform convulsion.

ETIOLOGY.

Adrenal insufficiency is usually observed in individuals between 20 and 30.

1.—It may be the result of chronic lesions of the adrenals: syphilis, cancer, and particularly tuberculosis. Tuberculosis is the most common cause of adrenal insufficiency. It nearly always causes slow syndromes of the disease, but as a result of the progressive extension of the lesions it also causes acute syndromes.

The tuberculous lesions of the adrenals are sometimes latent and some individuals appear in perfect health at the time they are suddenly overwhelmed with severe symptoms. In reality adrenal insufficiency already existed in a latent form and it is often a minor factor: overwork, traumatism (accidental or operative), an acute tonsilitis, which cause new lesions in these already degenerated glands. The healthy portions up to then sufficient, are then destroyed. Again one of the causes already mentioned, introduces into the organism an excess of poisons which the antitoxic function of the defective gland is incapable of neutralizing; then the acute symptoms of adrenal insufficiency develop.

II. ADRENAL INSUFFICIENCY IS THE RESULT OF AN ACUTE INFECTION:

Diphtheria, typhoid fever and scarlet fever are three diseases which most often cause it.

(*a*) Diphtheria.—Certain sequels of severe diphtheria described under the name of late infectious syndrome (Marfan), cardio gastric syndrome (Sevestre) and believed to be due either to a toxic myocarditis, or to a bulbar lesion or to a neuritis of the vagus, but must be recognized as an adrenal insufficiency. They are characterized by pallor of the face, vomiting, abdominal pain, cardiac disturbances: tachycardia, arythmia, inequality of the pulse and end with sudden death. There is extreme hypotension and the white line is quite marked. The experimental observations of Oppenheim and Loeper and the clinical data of Martin and Darre, of Hutinel and others have proved quite conclusively the adrenal pathogenesis of the late accidents following diphtheria.

(*b*) Typhoid Fever.—Sergent and Castaigne have shown that certain phenomena observed in the course of typhoid fever and characterized by asthenia, feeble cardiac contractions, soft and weak pulse, drop in blood pressure, which usually are considered as symptoms of myocarditis are really symptoms of adrenal insufficiency. They are, furthermore, better improved by suprarenalin than by cardiac tonics. Sudden death during convalescence considered by some to be due to myocarditis and by others to be a cardiac reflex, of intestinal origin, can be the result of adrenal insufficiency.

(*c*) Scarlet Fever.—Hutinel has insisted on the adrenal pathogenesis in the severe syndrome of scarlet fever. It is also to this adrenal insufficiency that we have to place the blame of sudden death in this disease (Moizart Gouget and Dechaux).

(*d*) Adrenal insufficiency can complicate all the infectious diseases: pneumonia and broncho pneumonia, influenza, measles, erysipelas (Lesne), cholera (Naame), dengue (Koury), certain symptoms of pernicious malaria (Paisseau and Lemaire), various septicemias. The severe erythemata, which occur in the course of infectious diseases, often are indicative of an acute inflammation of the adrenals (Ribadeau-Dumas and Harvier).

The acute infections determine an adrenal insufficiency by causing massive lesions of the adrenals. If the lesions are not as extensive or as deep, the clinical phenomena are not as severe and less definite, because they are hidden by the causative disease.

III. ADRENAL INSUFFICIENCY FOLLOWING VARIOUS FORMS OF INTOXICATION.

Alimentary poisoning, poisoning by mushrooms, by suffocating gases, by ether and particularly by chloroform (Delbet, Herrenschmidt and Beauvy) can cause adrenal insufficiency by the intermediary of lesions of the suprarenal capsules.

DIAGNOSIS.

1.—The diagnosis of slow adrenal insufficiency is always difficult. They are particularly liable to be overlooked in cases in which there is no pigmentation, as in the pure cases of adrenal insufficiency. A number of pathological processes have a very similar symptomatology: asthenia, hypotension, gastro intestinal disturbances and anemia are found in pulmonary tuberculosis, latent cancer, certain cases of neurasthenia, certain diseases of the blood as anemia, leukemia, etc. Any morbid process associated with asthenia and hypotension, is indicative of adrenal organo therapy and its adrenal origin can be suspected if there is some improvement by this type of medication.

2.—When symptoms of acute insufficiency occur during the course of an infectious disease, the diagnosis is easier. During convalescence from diphtheria, the symptoms are as a rule so definite that no hesitancy is permitted. In the course of typhoid fever, however, the signs are often hidden by the primary disease. Typhoid myocarditis presents circulatory symptoms: tachycardia and hypotension analogous to those of an inflammation of the adrenals. The presence of the white line, of abdominal pain, vomiting, and pallor are in favor of an adrenal involvement. Cyanosis, congestion of the lungs, the increase in the size of the liver, are more indicative of a myocarditis.

3.—The acute adrenal insufficiencies occurring without any definite etiology can simulate: poisoning (voluntary or accidental), enteritis, intestinal obstruction, appendicitis and acute pancreatitis. When nervous symptoms are present it may simulate apoplexy, coma or meningitis.

4.—When the abdominal or nervous symptoms, constitute, together with sudden death, the only signs of adrenal insufficiency, it is impossible to make the diagnosis during life. We must remember that lesions of the adrenals are frequently found in sudden deaths. For this reason in any medico legal case, the state of the adrenals must be carefully investigated, for certain incidents, such as, traumatism, surgical operations, might seem to be the cause of death, while in reality the patient had had a latent adrenal insufficiency unsuspected during life.

PATHOLOGICAL ANATOMY.

At autopsy of patients having died from the results of a slow adrenal insufficiency, many different types of adrenal lesions have been found, in particular tuberculous lesions, which will be studied with Addison's disease.

Acute insufficiency is determined by different kinds of lesions:

1.—Hemorrhages of the Adrenals.—These are very frequent in infectious diseases. They are more often bilateral and vary from punctiform hemorrhages to massive ones; the gland is swollen, dark red in color and showed on incision a marked congestion and hemorrhages visible to the naked eye in the cortex. In severe cases they are changed into hematoma, barely surrounded by a shell of cortical tissue. Some cases have even been reported of rupture of the capsule and to eruption of the blood in the cellular retroperitoneal tissue.

2.—Change of the Adrenals into Cavities.—These also occur quite frequently during infections; it is characterized by a softening or a destruction of the medullary substance. It is often unilateral and the other gland appears healthy although showing marked changes histologically.

3.—Occasionally, the gland has a normal appearance. It is hardly enlarged and of a dull white color. In spite of this, the histological lesions are quite extensive.

Three types of lesions have been found in variable proportions:

1.—Vascular lesions, varying from simple congestion to hemorrhages.

2.—Interstitial lesions characterized by a leukocytic infiltration, sometimes diffuse, sometimes localized to certain points forming small infectious nodules or microscopic abscesses where bacteria can be found.

3.—Degenerative cellular lesions in some places terminated by complete necrosis. Various stains bring out these changes quite well.

These various lesions are found both in infections or in intoxications, whatever their etiology.

In a general way it can be said, that according to the nature of the toxic agent or the duration of the infection, the alterations shown by the adrenals are: in slow intoxication or mild infections, leukocytic lesions and in acute infections or intoxications, vascular lesions associated with variable cellular lesions according to the disease.

TREATMENT.

Adrenal insufficiency is a serious condition, as there is always a possibility of sudden death. It gives the infectious disease a bad outlook. It can, however, be considerably improved or even cured by organo therapy.

Adrenal organo therapy can be administered in three different ways:—

(*a*) The fresh gland, preferably that of a calf, is chopped up in doses of 2 to 5 grams. It is generally not well tolerated.

(*b*) Suprarenal powder of the total extract of the desiccated gland.

(*c*) Suprarenalin.

INDICATIONS.—From a physiological point of view, we are led to believe that the total extracts are indicated in the cases in which toxic symptoms predominate, while suprarenalin which keeps up the vascular tonus, and the arterial pressure, is indicated in those cases in which the cardio vascular disturbances are the most marked. As a matter of fact, suprarenalin is advisable in all cases. It has the advantage of being easily manipulated. The extracts of the adrenals have a variable activity; they can however give better results when the asthenia, and the gastric and nervous disturbances are particularly marked.

METHOD OF ADMINISTRATION.—The best preparation to use is a solution of 1 to 1000 of epinephrin. The method of administration is to be taken into consideration, for suprarenalin is very toxic when injected intravenously; it is much less so subcutaneously and practically harmless when given by the gastro intestinal tract.

1.—By mouth, suprarenalin gives very good results, particularly in the cases of cardio vascular asthenia during infectious diseases, providing it is given in sufficiently large doses: 20 to 100 drops of a solution of 1 to 1000 daily. Whatever the daily doses, it must be given fractionally during the day, because of the ephemeral action of suprarenalin. This type of medication can be administered without any bad effects for several weeks.

2.—By subcutaneous or intramuscular injection. From ½ to 2 ccs. of a solution of 1 to 1000 can be given daily in fractional doses. Subcutaneous doses have two inconveniences. They sometimes cause severe pain and they will act too rapidly. For this reason medication in this manner must be kept for special cases to avoid serious symptoms.

There is, however, an excellent method of administering suprarenalin subcutaneously, and that is, as advocated by Josue, a dilute solution of suprarenalin. It is usually prepared by adding to 250 to 500 cc. of normal saline, 1 milligram of suprarenalin and 1 centigram of novocain to prevent pain.

3.—By rectal administration by means of the Murphy drip.

METHODS OF ADMINISTRATION OF THE TOTAL EXTRACTS.

The total adrenal extract can be administered by mouth in doses of from 0.30 to 0.60 centigrams daily. The maximum dose should rarely be over 0.90 centigrams. It is best to divide the doses into three administrations daily.

The total extract can be administered in doses of 0.1 daily hypodermically. The subcutaneous administration is sometimes more active than the oral therapy. For cases of slow adrenal insufficiency one of these methods can be kept up for a month or two, by series of ten days of treatment, interrupted by rest periods of from 5 to 10 days.

II. ADDISON'S DISEASE.

The disease described by Addison is characterized by progressive asthenia, anemia and a pigmentation of the skin.

In his first report in 1855, Addison believed that this disease was due to a tuberculosis of the adrenals. Three years later he brought out the fact that there was a co-existence of tuberculous lesions of the adrenals and of the semi lunar ganglia of the greater sympathetic. For many years Addison's disease was explained by means of two theories.

1.—Glandular theory, based on the anatomical observations of Addison and the experimental researches of Brown-Sequard, who reproduced the disease, less the pigmentation, by removing the adrenals.

2.—The nervous theory advocated in France by Jaccoud, Lancereaux and Brault. They believed the disease was due to an alteration of the sympathetic. The lesions of the gland stay latent until the filaments of the abdominal sympathetic are affected.

The investigations of Sergent and Bernard have established the fact that Addison's disease is in reality a double syndrome: slow insufficiency of the adrenals and irritation of the solar plexus or the sympathetic, the latter explaining the pigmentation. The pigmentation is not of hematic origin; it does not contain any iron. It is a normal skin pigment and we know that the sympathetic is the regulating nerve of the skin pigmentation. The stimulation of this nerve causes a hypergenesis of the pigmentary cells. The pigmentation does not always come from the stimulation of the extra adrenal sympathetic (solar and semi lunar ganglia). It may be the result of an alteration of the ganglia and nerve in the adrenals, which are so numerous in the medulla that the latter is considered as a nerve layer in close relation with the adrenalogenous cells (see physiology of the sympathetic).

From these three main facts result:

1.—That melanodermia is the main symptom of the disease described by Addison. "Without any melanodermia, there is no Addison's disease," says Sergent.

2.—Tuberculosis is the most frequent cause of Addison's disease, but not the only one (cancer or syphilis may also be the etiological factor).

3.—Adrenal tuberculosis and Addison's disease are not synonymous, since, as we have just seen that tuberculosis of the adrenals manifests itself by a syndrome of adrenal insufficiency without any melanodermia.

SYMPTOMS.

We will use as an example a case of Addison's disease of tuberculous origin. This condition is nearly always primary and occurs in individuals between 15 and 30 who may previously have evidence of tuberculosis, but as a rule no active pulmonary lesion.

The onset is very insidious: Feeling of lassitude, weakness, loss of strength, are the first manifestations which are noticed by the patients; then the symptoms become more definite and the disease as it progresses begins to show evidences of adrenal insufficiency; asthenia, arterial hypotension, white line, circulatory disturbances, gastro intestinal symptoms, lumbar pains; all signs of deficiency of the glandular function.

The most characteristic sign is the melanodermia. It usually does not appear until after the asthenia has set in. It nearly always starts in the regions already pigmented, such as, the genital folds at the level of the hips, on the internal surfaces of the arms and around the breasts, then it becomes generalized and manifests itself in the regions exposed to the air; the face, the neck, the back of the hands. It is often more marked at the beginning of the disease in the regions irritated by rubbing such as, by a collar, corsets, etc., and at the level of scars, burns, etc. These irritated spots of the skin are the usual starting points of the pigmentation and it is by basing themselves on this fact that Jacquet and Tremolieres have suggested bringing it out when it is not very definite, by an artificial irritation of the skin, such as, a plaster or cupping.

The character of Addison's disease pigmentation is very peculiar. It is made up of brownish spots. They may be uniform in color or contain darker pin head spots. The skin in the neighborhood is dry and parchment like.

At first the pigmentation may be very discreet, but as the disease progresses, it becomes more generalized and the skin takes on a darker and darker appearance, more marked in the regions first affected. In some places loss of pigment occurs, giving whitish spots resembling vitiligo. The pigmentation may involve the hairs, which may change from blonde to black; the nails take on a yellowish tint. The mucous membranes are nearly always involved. On the buccal mucous membrane are seen bluish like spots, as those sometimes seen in certain races of dogs. This pigmentation may affect the lips, the gums, even the conjunctiva.

EVOLUTION.

Addison's disease has a progressive evolution. The patient becomes anemic early, the muscles atrophy rapidly and this amyatrophism at the beginning, contrasts with the conservation of the adipose tissue. Then these patients become cachectic. They are extremely sensitive to cold and their temperature is often subnormal.

Sometimes, under the influence of organo therapy, the evolution is interrupted by long periods of remission, then the disease goes on so that the duration of the disease rarely extends over a few years. Certain rare cases only last a few months. The patient dies of cachexia, with symptoms of cardiac collapse preceded by diarrhea.

Addison's disease can also terminate suddenly. This is usually brought about by excessive fatigue, an operation, chloroform anesthesia, or even a slight infection. The glandular deficiency is such that the glands cannot neutralize the slightest excess of toxins circulating in the organism. Death occurs in a few hours or a few days.

Sudden death is always possible at any time during Addison's disease.

CLINICAL FORMS.

Many writers describe as abortive cases of Addison's disease some characterized by an absence of melanodermia. These cases studied by Dieulafoy and Bressy really belong to simple adrenal insufficiency and for this reason should not be included under Addison's disease. They refer to cases having active or latent tuberculous lesions of the adrenals, who, due to some slight accident, die suddenly or give the appearance of acute poisoning or peritonitis.

In certain cases, such as, the gastro intestinal, painful or asthenic type, the melanodermia develops late in the disease. Inversely, there is a melanodermic form characterized by the fact that the pigmentation is the first to appear.

The symptoms of adrenal insufficiency, particularly asthenia, only appear secondarily and for quite a while are only very mild. These cases usually have minor lesions, nearly always limited to the peripheral layers of the adrenals. Addison's disease can be associated with other glandular lesions, in particular, to thyroid syndromes: Basedow's disease or myxedema.

In some cases of tuberculosis a slight pigmentation is sometimes observed. It is made up of small disseminate spots, light brown in color, located on the lateral part of the neck around the nipples and in the region of the deltoids. The pigmentation does not invade the face, the hand or the mucosa. The symptoms of Addison's disease are attenuated. These patients are more anemic, weaker and have a lower blood pressure than the ordinary cases of tuberculosis. In other words, they have the mild type of Addison's disease which has been described by Lafitte Moncany and Bonnet under the name of Addisonism.

DIAGNOSIS.

The diagnosis of Addison's disease is made by the pigmentation.

However, pigmentation of the skin or mucosa occurs in a series of affections, foreign to a pathology of the adrenals, but there are certain characteristics which allow us to differentiate it from Addison's disease:

1.—In malaria the pigmentation is uniform, the color is dirty gray and does not involve the mucosa.

2.—In pigmentary cirrhosis, the pigmentation has a slate-like color, resembling mercury ointment.

3.—In arsenical intoxication (professional or medicated) the pigmentation resembles very much the pigmentation of Addison's disease. It is generalized but predominant on the trunk and the roots of the limbs; it does not involve the uncovered extremities, the genital organs or the mucosa.

4.—In pityriasis, the pigmentation is more often on the back of the neck, on the shoulders, at the level of the belt and of the limbs. The skin is marked with liniary excoriations due to scratching and white lines,which are scars.

Pityriasis of tramps sometimes causes a pigmentation of the mucosa (Thibierge). The diagnosis may be in doubt for several days, for these individuals may be so tired that they appear asthenic. It, however, clears up very rapidly with rest.

5.—In syphilis the pigmentation which is sometimes found, at first starts in the region of the neck, then spreads to the body and limbs; even when diffuse it still keeps its characteristic areolar appearance; it looks like a net work, dirty yellow in color, surrounding areas of non pigmented or healthy skin.

6.—Pigmentation of the mucosa occurs after mercury treatment or in certain races (Roumanians, Tzigans, Bohemians) and in these cases is independent of all pathological affection.

The objective characteristics of the pigmentation of Addison's disease is, therefore, sufficient to distinguish it from other forms of pigmentation of the skin or mucosa.

PATHOLOGICAL ANATOMY.

The lesions found at autopsy in this disease are as follows:

1.—Tuberculosis of the Adrenals.—This is the most common cause. The tuberculosis may be primary (infection through the blood stream) or secondary to a renal, diaphragmatic or pleural tuberculosis. The lesions are quite often bilateral and show many different anatomical changes.

(*a*) *Isolated Tubercles.*—The gland is increased in size, irregular, but free from all adhesions. A section shows one or more tubercles in various stages of evolution. Sometimes in the beginning stage, in other cases caseated or calcified. These tubercles are more often in the medulla and are surrounded by a shell of cortical substance.

(*b*) *Caseation.*—The gland is swollen and irregular. It adheres to the surrounding structures. Its weight may be as much as 20 to 30 grams. On incision it shows a translucid glassy appearance, resembling putty. As a rule the caseation has involved everything but the periphery of the gland.

(*c*) *Sclerosis.*—In these cases the glands are absolutely unrecognizable. They are surrounded just as the tuberculous kidneys, by a fibrous fatty layer and transformed in a fatty substance full of cavities containing pus or caseated material, or they may be sclerosed and atrophic.

These last two types are the most frequent.

(*d*) *Cold Abscess of the Adrenals.*—These are very rare. The gland contains one or more pseudo cysts, with very thin walls, containing a purulent fluid.

Histological examination reveals tuberculous lesions (real tubercles with giant cells, bunches of lymphocytes containing tubercle bacilli). To these glandular lesions are associated, more or less constantly, tuberculous lesions of the sympathetic and the semi lunar ganglia.

Sometimes the celiac and periaortic ganglia are swollen and caseated and compress the solar ganglia and nerves which become atrophic and disappear so that it is difficult to find them, even by histological examination.

2.—SCLEROSIS OF THE ADRENALS.—The origin of these changes is very variable. An old infection (Sergent) a lesion in the neighborhood, can be the cause. It may also be the result of tuberculosis (Sezary).

The adrenals are large and adherent to the liver, kidneys, gall bladder and have a white color. They are made up of a hard tissue, which cuts with difficulty. Histological examination reveals many strands of connective tissue, causing a separation and atrophy of the cortical cells and sometimes even penetrating into the medulla.

At the same time are noticed congestive lesions, infectious nodules or cellular degenerations which show an acute inflammation on top of old lesions.

3.—ADRENAL SYPHILIS.—Very rarely syphilis is the cause of lesions of the adrenals: gumma, diffuse sclerosis, etc.

4.—CARCINOMA.—Primary or secondary cancer (epithelioma, etc.) is rarely bilateral. For this reason, it is only very rarely the cause of Addison's disease.

TREATMENT.

Except in the very rare cases in which Addison's disease occurs in syphilitics and in which specific treatment is indicated, the treatment is purely symptomatic.

1.—Organo therapy, directed against the adrenal insufficiency is very important.

Suprarenalin can be used in the same manner as in cases of adrenal insufficiency; the total extract seems preferable either as the fresh gland (of sheep or calf), starting at first with half then a whole gland, or in the form of dried extract in doses of from 0.60 to 0.90 centigrams daily.

If medication by mouth is counterindicated, by reason of the gastric intolerance, so frequent in Addison's disease it is possible to administer subcutaneously the glycerin extract of the adrenals of sheep in doses of 1 to 5 ccs., diluted in normal saline (10 to 20 ccs.) to make it less painful.

It is important, whatever the medication employed, to start in as soon as possible and to keep it up for a long period of time. The results are often only noticeable in many cases several months afterwards. The results are, furthermore, far from being constant. Some manifest a real intolerance for organo therapy; they have nausea, vertigo, waves of heat. Glycosuria tremors have been noted after the administration of adrenal extracts in patients with Addison's disease. In others, even when treated at the beginning of the disease, organo therapy is of no value. Others, however, derive considerable benefit from the treatment. Remissions lasting several years have been obtained. In the majority of cases there is simply an improvement of certain symptoms; the blood pressure goes up, asthenia decreases, the gastro intestinal disturbances disappear. The pigmentation on the other hand is rarely influenced by this treatment.

2.—TREATMENT OF THE PAINS AND GASTRO INTESTINAL DISTURBANCES.—The pains are sometimes severe enough to require local treatment. Counterirritation is preferable to an analgesic, for all toxic medication must be given with extreme care in Addison's disease.

If the vomiting is not improved by organo therapy counterirritation in the pit of the stomach will help. Sometimes chloroform water or cocaine will prove to be beneficial.

3.—GENERAL AND HYGIENIC TREATMENT.—This is very important. These patients must avoid all fatigue. The slightest infection may be the starting point of severe symptoms of adrenal insufficiency. The usual diet of tuberculous patients is advised for these patients. Arsenic, often given in tuberculosis, must, however, be avoided or only given very cautiously. Phosphates are supposed to be beneficial.

III. MILD ADRENAL INSUFFICIENCY.

This condition corresponds to an attenuated adrenal secretion and may be due to many causes.

The various clinical manifestations are as follows:

1.—In tuberculosis; mild adrenal insufficiency explains:

(*a*) The asthenia of certain patients, out of proportion to the tuberculous lesions.

(*b*) The hypotension which is so often seen and which has been so much insisted upon by such clinicians as Marfan, Potain, Teissier and which must be taken into account in the prognosis.

(*c*) The evolution of the tuberculosis.—Sergent, starting from the hypothesis that recalcification is an important factor in tuberculosis and having shown that adrenal extract is a powerful adjunct to recalcification, concludes that a decrease in the adrenal secretion plays an important part in the progress of tuberculosis.

2.—In Patients Suffering from Asystole, according to Josue, adrenal insufficiency appears as the terminal ending of asystole. To the signs of cardiac insufficiency are added: asthenia, hypotension, the white line. At autopsy, the atrophy of the adrenals contrasts with the hypertrophy of the myocardium.

3.—In Nephritics, the syndrome of adrenal insufficiency and even the syndrome of Addison's disease is sometimes the ending of this disease. Cachexia, pigmentation and particularly hypotension, then follows a marked hypertension which has lasted months or years (Castaigne). It looks as if the decrease in the adrenal function was due to a previous period of hyperfunction.

4.—Mild adrenal insufficiency in *post operatives or pregnant women.*—Certain symptoms of operative shock which manifest themselves by small, feeble pulse or acute dilatation of the stomach characterized by abundant vomiting, and even hemorrhages with tendency to collapse can be traced to an adrenal insufficiency, for these symptoms will improve promptly under suprarenalin. The same is true in certain cases of vomiting of pregnancy which are cured by adrenal organo therapy (Sergent and Lian).

5.—Adrenal Debility.—Adrenal debility (Sergent) is very closely related to mild insufficiency. It can be congenital and thus explain the physical and psychic state of certain children; slow, apathetic, always tired, emaciated, having a low blood pressure and which are greatly helped by organo therapy.

It may be acquired following an infection having involved the adrenals. Patients recovering from typhoid or severe scarlet fever are for a long time asthenic, with a low blood pressure and an anemia. They are really suffering from a hyposecretion of the adrenals and are improved by organo therapy.

This conception of congenital or acquired adrenal debility helps to explain the intolerance of certain subjects to the administration of arsenobenzol (Milan) or antityphoid vaccination (Lian, Loeper, Mery and Halle). The efficacy, both as a preventative and as a curative of suprarenalin proves the origin of these phenomena.

6.—ADRENAL INSUFFICIENCY AND MUSCULAR SYNDROMES.—The muscles utilize adrenalin. Carnot and Josserand have shown that in order to produce the same increase in the arterial pressure, it was necessary to give three times as large a dose in the artery as intravenously, because suprarenalin when injected in the artery goes through the muscles which utilize it.

In the same manner, a dose of suprarenalin sufficient to raise the blood pressure when injected intravenously is without effect when injected into the arteries.

This enables us to understand how muscles deprived of suprarenalin, suffer in their nutrition (myasthenia) and in their functions (amyotrophy). We have seen how certain tuberculous patients suffering from slow adrenal insufficiency present a marked emaciation of the muscles, a diffuse amyotrophy (Sezary) which contrasts with the amount of subcutaneous fat.

Certain cases of myasthenia which are included in the syndrome of Erb-Goldflam, characterized by a muscular asthenia, (weakness of the muscles, tendency to be easily tired), either diffuse or limited to certain muscles of the face, are probably due to some adrenal disturbance. They improve under adrenal medication, alone or combined, with thyroid or pituitary extract.

To these muscular conditions we can liken some of these pseudo paralyses found in chorea, described by Sergent and Bosset under the name of soft chorea and believed to be due to an adrenal insufficiency resulting from the abundant muscular poisons, formed by the constant movements of choreic patients.

The knowledge of these cases of adrenal insufficiency has not only a theoretical but a practical application. It explains the pathogenesis of many morbid conditions, which can only be helped by organo therapy.

CHAPTER VI.

SYNDROMES OF HYPERFUNCTION OF THE ADRENALS.

A hyperactivity of the adrenals manifests itself clinically by a cardio vascular syndrome characterized by hypertension associated with a hypertrophy of the heart. The rise is in both the systolic and diastolic pressure. It is accompanied by a hypertrophy of the left ventricle which is manifested by the pushing outwards and downwards of the apex of the heart, a powerful shock against the thoracic walls, a marked aortic sound and a galloping sound on the left side. The examination of the heart shows a very marked hypertrophy (Widal and Raulot-Lapointe).

The various clinical manifestations of this cardio vascular syndrome will be studied in some other chapter. We will only mention that clinically it appears in three main forms.

1.—Pure Form.—The arterial hypertension constitutes the only clinical manifestation, which is discovered accidentally in plethoric subjects or young people with great physical and mental activity. In other cases, the patients are pale and emaciated and have symptoms of lassitude and asthenia.

The arterial hypertension is permanent and irreducible. There are at certain times paroxysms caused by vascular spasms at the level of various organs, in particular of the nervous system. Symptoms then manifest themselves; such as, encephalitis, amaurosis, aplasia, Jacksonian epilepsy, which are transitory and nearly always influenced by hypotensive medication; they cease with the spasm.

2.—FORMS ASSOCIATED WITH CHRONIC NEPHRITIS.—With the arterial hypertension is noticed signs of arterio sclerosis and atheromata: dilatation of the aorta, systolic or diastolic murmur of aortic insufficiency.

The evolution of these various syndromes is variable. Some patients die of vascular hemorrhages (cerebral hemorrhages, epitaxis, hemorrhages of the mucosa). Some die of renal complications or of uremia. Others finally die from symptoms of failure or cardiac insufficiency. Two complications are particularly important.

(*a*) Acute edema of the lungs, in patients with renal or aortic lesions.

(*b*) Glycosuria, which is usually transitory and mild.[1]

The two most important causes of these syndromes of adrenal hyperfunction are:

1.—NEPHRITIS.—Be it some infectious nephritis or a chronic nephritis.

2.—MERCURY POISONING.—These cases nearly always show a plain hypertension or associated with either signs of nephritis or arteriosclerosis.

* * * * *

The understanding that adrenal hyperfunction can be responsible for chronic affections; such as, hypertension, cardiac hypertrophy, vascular lesions (atheroma and arterio sclerosis) and also temporary affections; such as, acute edema of the lung and glycosuria is proved by two different kinds of facts.

1.—ANATOMICAL FINDINGS.—Manetrier, Vaquez, Aubertin, Gaillard, Widal, Boidon and Josue have shown at autopsies of patients having atheromatous or nephritic lesions with cardiac hypertrophy, some cases with adrenal hyperplasia. The two glands are increased in size and in weight. They are puffed out, deformed and have an adenomatous appearance, which is always an indication of glandular hyperfunction. The hyperplasia is most marked on the medullary layer in some cases, while at others the cortex is chiefly affected. When the medulla is hypertrophied the explanation of hypertension is simple, since this tissue contains all the suprarenalin forming cells. When, however, the hypertrophy is limited to the cortex, the explanation is more difficult. According to Abelous and Soulie, the cortex really secretes suprarenalin, which is simply accumulated by the medulla, and Josue has shown that the extract of the cortex had the property of raising the blood pressure. The majority of investigators, however, refuse to believe that the cortex secretes suprarenalin and insist that after death suprarenalin diffuses from the medulla into the cortex. Langlois has brought out the theory that by changing the poisons of muscular origin, the cortex prepares the substance from which the medulla elaborates suprarenalin.

---

[1] Test for adrenal hyperirritability:—Subcutaneous injection of 1-1000 adrenalin. Thirty minutes after injection there will be a rise in blood sugar.

2.—EXPERIMENTAL OBSERVATIONS.—The excess of suprarenalin secretion explains all the following clinical manifestations:

(*a*) Suprarenalin has certain definite hypertensive and vaso constrictor properties; it plays an important part in the regulation of the blood pressure.

(*b*) Josue has shown that the injection of small doses in the veins of a rabbit causes a hypertrophy of the heart and atheromatous degeneration of the arteries.

(*c*) In large doses it will bring on acute edema of the lungs comparable to that observed in nephritis. This edema can be a consequence of a hypersecretion of suprarenalin (Josue).

(*d*) The subcutaneous, intravenous or intraperitoneal injection of suprarenalin causes the appearance of sugar in the urine of certain animals (Blum).

(*e*) Adrenal hyperplasia can be caused experimentally by toxic substances, in particular, by lead (Bernard and Bigart). Lead causes at the same time atheromatous lesions and hyperactivity of the adrenals (Gouget). On the other hand, Dopter and Gouraud, then Darre, have shown the frequency of adrenal hypoplasia during the course of uremia or experimental nephritis. Schu and Wiesl are said to have found it present in the serum of animals having nephritis with hypertension.

* * * * *

The relationship between hyperplasia of the adrenals and its clinical consequences: hypertrophy of the heart, hypertension, and vascular lesions, has given rise to several interpretations.

1.—THE HYPERPLASIA OF THE ADRENALS IS PRIMARY.—Certain intoxications, certain infections (lues, malaria), certain types of nephritis also cause a hyperplasia of the adrenals followed by arterial hypertension, cardiac hypertrophy and arterio sclerosis.

2.—THE ARTERIO SCLEROSIS IS PRIMARY AND THE ADRENAL HYPERPLASIA SECONDARY.—Arterio sclerosis is not always of adrenal origin. It may be infectious or toxic, or secondary to some kidney lesion. Adrenal hyperplasia then occurs to keep up the cardio arterial tonus, which must be raised to overcome the vascular lesions, according to the mechanism indicated by Gouget.

3.—ADRENAL HYPERPLASIA CAN BE SECONDARY TO CARDIAC LESIONS. ACCOMPANIED BY HYPERTROPHY OF THE HEART.—According to Josue, primary cardiac hypertrophy exaggerates the myotonic function and causes, by a sort of physiological adaptation, an adrenal hyperplasia which becomes the starting point of arterio sclerotic lesions.

Adrenal hyperplasia, cardiac hypertrophy, arterio sclerosis constitute an anatomical clinical syndrome which Josue has called adrenal vascular syndrome.

Basing themselves on these pathological considerations, Zimmern, Cottenot, Sergent and others, have applied the principle of inhibiting the action of the glands by radio therapy. This therapeutic measure, not yet much in use, seems to have given good results in certain cases of hypertension.

CHAPTER VII.

ADRENAL TUMORS AND DYSTROPHIES OF ADRENAL ORIGIN.

There are two varieties of adrenal tumors.

1.—Benign tumors, which are only discovered accidentally at autopsy and have no clinical history. Fibromata, hydatid cysts are exceptional, adenomata more frequent. They are found in individuals having died from numerous causes (pneumonia, nephritis, tuberculosis, atheroma, etc.).

2.—Malignant Tumors. Some are secondary to a carcinoma in the neighborhood (kidney, pancreas, stomach) and are without clinical interest; the others are primary and develop from the adrenal tissues.

From an anatomical point of view these primary malignant tumors are carcinomata, which nearly always develop in the cortex, or sarcomata which are rather large in size and filled with blood. These are most commonly found in the young.

From a clinical point of view, these tumors are sometimes latent and only discovered at autopsy. In other cases, they constitute abdominal or lumbar abdominal tumors, the clinical diagnosis of which is very difficult. They are rounded, lobulated, irregular and of a hard consistency, adherent and sometimes as large as an infant's head. They have a lumbar pedicle and are as movable as renal tumors. In other cases they are absolutely immovable and do not rise on inspiration. Sometimes they are associated with ascites and with a collateral abdominal circulation, edema of the lower extremities and of the region below the umbilicus, when the inferior vena cava is compressed.

They cause pressure pains: subhepatic pain, lumbar pains, unilateral or girdle like, continuous or in paroxysms; gastro intestinal disturbances; vomiting, attacks of diarrhea or obstinate constipation and quite often respiratory difficulty.

The evolution is usually very rapid. The patients may die very suddenly. In the majority of cases they lose weight, become cachectic and die in coma. Pigmentation of the skin is not common. Sometimes death occurs from extension of the tumor to the neighboring organs or a generalization of the carcinoma.

The diagnosis is very hard, for two reasons; for one, these tumors have no definite symptomatology; the other, that they are so rare that nobody suspects an adrenal tumor. At first, because of the lumbar pain a diaphragmatic, or subphrenic affection is suspected, or even Pott's disease. The presence of ascites and of edema of the lower limbs can hide the tumor and lead to suspect a hepatic lesion. When a lumbar abdominal tumor is distinctively made out it is often mistaken for a kidney tumor, or if the digestive symptoms are prominent with a neoplasm of the pylorus or colon.

The only treatment is surgery. The removal of the tumor is possible, but is dangerous. Survival is rare and re-occurrence is the rule.

GENITO-ADRENAL SYNDROME.

To the study of tumors of the adrenals must be added a special dystrophy described under the name of genito-adrenal syndrome.

In 1905 Bullock and Sequeira, then Guthrie in England drew attention to the relationship which existed between the adrenals and of the adipose tissue, genital organs and hairs. In France, Guinon Apert presented successively observations of genital dystrophies associated with alterations of the adrenals and Gallais in 1912 described the genito adrenal syndrome.

This syndrome is found in the female sex (it is rare in men), more frequently in little girls between 3 and 11. There are two main types; adrenal pseudo hermaphroidism and adrenal virilism. There are also mild types of these two conditions.

I. ADRENAL PSEUDO HERMAPHROIDISM.

It is characterized by the co-existence in the same individual of the sexual organs of one sex and the genital glands of the opposite sex; the real sex of the individual being indicated by that of the genital glands.

For instance, an individual having feminine external genitalia and testicles is an external male pseudo hermaphrodite. An individual having ovaries and male external genitalia, is an external female pseudo hermaphrodite. The latter is the more common of the two observed in adrenal pseudo hermaphroidism.

These individuals, which in reality are women, are considered as men; they have a more or less well developed penis, with hypospadia, a well formed scrotum containing fat which is mistaken for the testicles. On rectal examination a prostate and even seminal vesicles are felt. But on autopsy or during the course of a laparotomy ovaries and tubes are found, sometimes a small uterus and vagina.

The secondary sexual characteristics evolute at puberty towards the male type; hairs appear on the abdomen and thighs; the mustache and beard grow very thickly; the voice, the character, the sexual instincts are those of the male; the penis can become erected; ejaculation is possible, but it is made up of a prostatic liquid.

This condition is incompatible with a long existence.

Some of these individuals have lumbar or thoracic girdle pains and examination reveals a lumbar tumor sometimes quite voluminous, which in children is mistaken for a sarcoma of the kidney or in adults for a tumor of the kidney.

In other cases, palpation reveals a tumor in the pelvis. In reality, we are dealing with an ovarian tumor of adrenal origin.

The diagnosis of adrenal pseudo hermaphrodism comes up: either in a young child having a perineal vulvar malformation with hypospadia and cryptorchidism and in which the sex is doubtful; or in adults at the time of puberty. We must remember that the great majority of cases are women in spite of their masculine appearance; that the presence of fatty masses in the scrotum is not indicative of the presence of testicles (we might also have supranumerary adrenal glands), that certain hematurias which are mentioned by the patients are really menses and that all pseudo hermaphrodites should have a careful examination of the abdomen and the pelvis.

II. ADRENAL VIRILISM.

This type differs from the preceding by the time of its appearance. It comes on at a time when the sexual differentiation is already completed, and in which the sex is not in doubt. It is characterized by modifications of the secondary sexual characteristics and develops parallel to the adrenal tumor.

Virilism may appear either in young girls after puberty, or in women after the manopause (late virilism), or in children.

1.—In the young girl or in the woman, the menses stop and the morphology changes: the hairs of the body develop excessively; a mustache develops together with a beard, hairs on the abdomen, on the thorax and the limbs, while at the same time the face takes on a masculine appearance. As regards the genitals the labia majora fall. The clitoris is hypertrophied, sometimes covered with a long prepuce. The voice becomes deeper, the muscular strength increases.

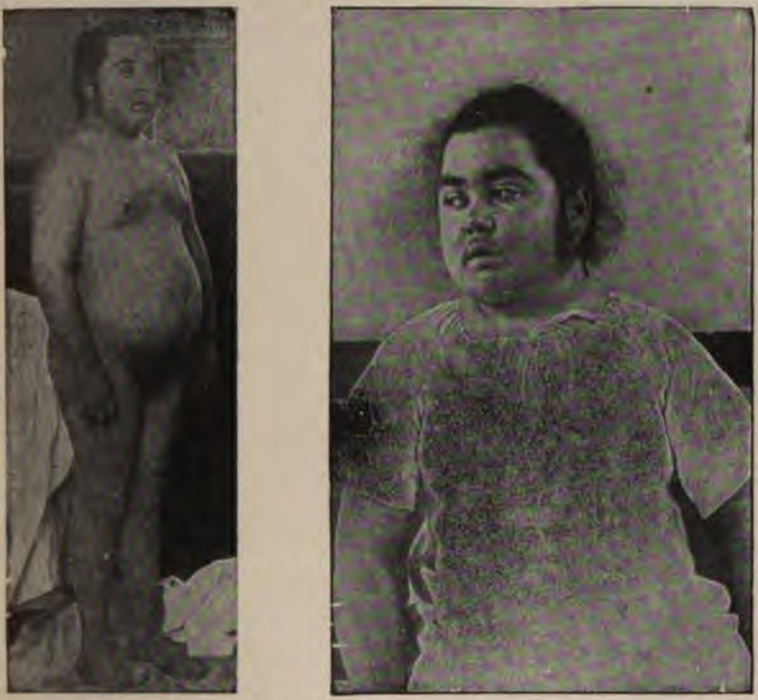


FIG. 4.—Hirsutism (Case of Drs. Guinon and Bijon).

The disposition changes; the patient becomes quarrelsome. In some cases, disturbances of mental activities occur; there may be loss of sexual appetite or inversion. Sometimes a certain amount of adiposity is noted, together with a slight glycosuria and sometimes a pigmentation, which gives a dirty gray appearance, limited to the forehead, axillia, the back or the superior limbs and differs in this manner from Addison's disease.

These symptoms of virilism with hirsutism (Apert) are the first to appear. Sometime afterwards appear symptoms of adrenal insufficiency: emaciation, extreme asthenia, hypotension, lumbar or thoracic girdle pains, and examination reveals the presence of an abdominal or pelvic tumor.

2.—In children, if we are dealing with a little girl between 5 and 6, they are characterized by an extraordinary amount of strength for their age. The genital organs (penis, testicle) are as large as those of a child of 14. Hairs appear, not only around the genital organs, but on the face, limbs and back.

Adrenal virilism is nearly always caused by a malignant tumor, which is fatal to the patient in a few months. Two years is the maximum.

III. ABORTIVE CASES.

In adult women or at the menopause, it is possible to observe the symptoms of an abortive form of genito adrenal syndrome, compatible with long life (due in these cases to benign tumors) and characterized by the disappearance of the menses, a somewhat noticeable adiposity, with or without pigmentation and a hypertrichosis of masculine systematization.

PATHOLOGICAL ANATOMY.

On autopsy of these patients are found in all cases tumors of the adrenal cortex and atrophic lesions of the ovaries. The adrenals show unilateral or bilateral variable lesions.

In the cases of pseudo hermaphroidism, one or both of the glands are lobulated and increased in size (whether dealing with plain hypertrophy or adenoma). In the cases of adrenal virilism are observed more often malignant tumors (carcinoma or sarcoma), sometimes of very large size and complicated by visceral metastasis. These tumors can develop at the expense of the accessory adrenals.

The ovaries are small, fibrous, full of small cysts. The Graafian follicles and the corpora lutea are few or missing.

In a recent observation of Tuffier there was atrophy of one ovary and tumor of the other.

PATHOGENESIS.

To understand the adrenal origin of these dystrophies it is necessary to recall that the adrenals and the genital organs gave a common embryological origin.

While the medullary substance of the adrenals arises from the nerve cells of sympathetic ganglia of the superior portion of the abdomen, the cells of the cortex are derived from a covering epithelium of the cœlom, which gives birth at the same time to the germinating cells of the testicle or ovary. Tourneux and Mulon have shown that the interstitial cells of the genital glands and the cells of the adrenal cortex have an identical histological structure, both contain pigments, lipochromes and phosphated lipoids.

The experimental researches of Theodosteff have established the fact that the removal of the ovaries in bitches is followed by a hypertrophy of the cortical cells of the adrenals. Raineri has found that the weight of the gland increased four times, a few months after the removal of the ovaries. Bevin observed in a young girl, whose menses had stopped, an adrenal tumor, the removal of which was followed by the return of menstruation. All these facts agree to prove that hypertrophy of the cortex of the adrenal is due to an atrophy of the ovary.

The hyperfunction of the adrenal cortex, due to a tumor, seems to disturb the development of the sexual characteristics. Coming on at the embryonic period, it may cause a pseudo hermaphroidism. Occurring after the complete formation of the genital organs, it gives rise to adrenal virilism.

From a practical point of view, we must remember that the observation of the syndrome of adrenal virilism means only: a tumor developing at the expense of the cortex of the adrenals. These tumors, due to the embryological reasons stated, can be located in any part of the abdomen or pelvis, even inside of the tissues derived from the organ of Wolff: kidney, ovary, etc., if they have as a starting point an accessory adrenal.

The observation of the genito adrenal syndrome necessitates not only the examination of the abdomen, but also of the pelvis and the labia which may contain ovarian tumors made up of adrenal tissue.

TREATMENT.

Medical treatment is of no avail and surgery is the only hope. The results depend on the location of the tumor. If an ovarian tumor develops from the accessory adrenals, the prognosis is favorable. This is not the case if the tumor involves the adrenal itself, for removal of the adrenal is a serious operation, the mortality of which is as high as 50%.

PROGERIA—SENILE DWARFISM

This syndrome can be placed next to the preceding ones, as its adrenal origin is very probable. It is very uncommon. The first case reported seems to have been that of Hutchinson in 1886. Hastings Gilford in 1896 described two cases under the name of *Progeria* (premature senility). Variot and Pironneau in 1911 have studied it under the name of senile dwarfism (see Fig. 5 and 6).

These cases are children who have the appearance of old men. A patient of Rand (1914) 8 years old, had the appearance of a woman of 65. The skin of the face was wrinkled, dry and faded. Growth was stopped. The patient of Variot, 15 years old, measured 1.02 meters and weighed 11 kilograms. The body was extremely thin. All those old children appear to have been scorched. The hairs and the eyebrows fall out and, to accentuate the resemblance to senility, the arteries are hard and rigid.

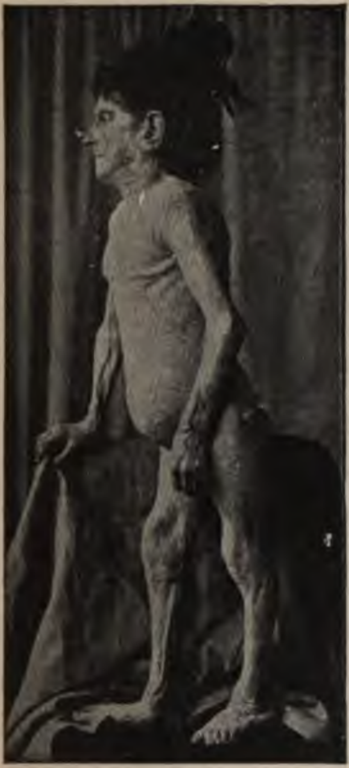


FIG. 5.—Senile dwarfism (Case of Rand).

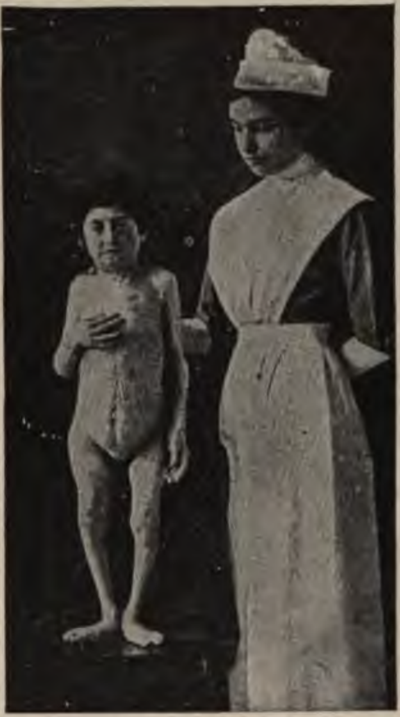


FIG. 6.—Senile dwarfism (Case of Rand).

In an autopsy performed by Gilford, the adrenals were atrophic and fibrous and at the same time there were marked lesions of the heart and the aorta.

CHAPTER VIII.

PATHOLOGY OF THE PITUITARY.

FUNCTIONS OF THE PITUITARY.

The pituitary is a gland or organ located at the base of the skull, in the cavity of the sella tursica. It is composed of two lobes; a large anterior lobe and a smaller posterior lobe. The latter, an invagination of the intermediary brain of the embryo, is still called nervous lobe. It is made up of a loose stroma, containing connective tissue and capillary blood vessels.

The anterior or epithelial lobe is a derivative of the bucco-pharyngeal ectoderm. It is made up of an anterior and posterior part separated by a hilum.

The anterior or glandular portion is made up of alveoli of variable sizes, containing cells which have various affinities for certain dyes, placed in a vascular network very well developed.

The posterior part, not very noticeable in man, consists of a layer of cylindrical cells or a ciliated epithelium, or of vesicles looking something like those of the thyroid and made up of a thick connective tissue wall line by cylindrical or ciliated epithelium.

The pituitary secretes substances brought in evidence by histology. They consist of fats, a coloidal material which is found between the strands of connective tissue, or in the vesicles. Experimentation also reveals the presence of a hormone in the posterior lobe called pituitrin or hypophysin, the action of which is comparable to that of suprarenalin.

The physiological action of the pituitary is obscure.

Its removal has given different results, according to the man investigating the condition. It is a very delicate operation, which is difficult to perform without injuring the neighboring nerve tissue. It seems, however, that the anterior and posterior lobes have different properties.

1.—Function of the Anterior Lobes.—The anterior lobe has something to do with the development of the skeleton and the growth of the body. Casseli, Fichera, Aschner, Ascoli and Leguani have found that the removal of the pituitary in young dogs nearly always causes death, two or three days after the operation. In the animals that survive, it is noticed a sudden cessation of growth, disturbances in ossification, an exaggerated adiposity and a genital hypoplasia. The genital organs keep their infantile characteristics and the seminal epithelium does not differentiate. The pituitary, therefore, controls, to a certain extent, growth and the genital organs. It has some action on metabolism of fat and the symptoms noticed on its removal are very similar to those found in certain tumors of the pituitary.

Inversely, Goetsch by feeding young rats with extracts of the anterior lobe, noticed a stimulation of growth and rapid development of the sexual glands.

2.—Function of the Posterior Lobe.—The injection of pituitary extract increases the blood pressure (Oliver and Schafer). This hypertensive action is accompanied by a decrease in the heart rate and strengthening of the systole. It is less intense, but lasts longer than that caused by suprarenalin. The cardio vascular function belongs to the posterior lobe; only the extracts of this lobe are active. Those of the anterior lobe being without any effect. It is believed that the secretions of the anterior lobe accumulate in the posterior one.

The action of the pituitary on the renal functions is known since 1901. Magnus and Schafer had noted that the extract of the posterior lobe has a definite diuretic effect, while the anterior lobe has no action on the kidney. These conclusions have not been confirmed by the investigations of von den Velden, of Farini, of Römer, or by the recent investigations of Moltzfeldt (1916) who considers that these extracts will instead cause a decrease in diuresis and a concentration of the urine. We can admit that the pituitary regulates the excretions of the kidneys, but the exact mechanism is uncertain. The pituitary secretion may act on the kidney, on the blood vessels, or on the epithelium. It can act independently or by the intermediary of the nervous system. At present, these questions have not yet been solved.

Experimentation brings out the evidence of a synergy of the pituitary and other endocrines. The pituitary hypertrophies after thyroidectomy, after castration, or after the removal of the adrenals. The pituitary extract has a vaso constrictor action on the blood vessels of the thyroid (Hallion).

PITUITARY SYNDROMES.

The pituitary syndromes are characterized by:

a.—Dystrophic conditions, which are:
  1.—Acromegalia.
  2.—Gigantism.
  3.—Pituitary infantilism.
b.—The others by general disorders of nutrition. These are:
  1.—The adipose genitalis syndrome.
  2.—Pituitary diabetes.

I. ACROMEGALIA.

Pierre Marie, in 1886, described this disease as a "peculiar non congenital hypertrophy of the limbs and head," and four years afterwards in the theses of his pupil, Louza-Leite, showed that it had some relation to disturbances of the pituitary.

SYMPTOMS.

The general aspect of acromegalia is so characteristic that the diagnosis is made on sight.

The face as a whole is increased in its length and takes the shape of an elongated oval. The forehead is low, the supraorbital ridges prominent, the eyes small. The nose increases in size in all directions and becomes enormous. The cheek bones are prominent, while the cheeks are sunken in. The ears are abnormally long.

The lips, particularly the lower one, fall down; they are thick and voluminous. The tongue is also involved in the general hypertrophy: it is thick, large, long and sometimes so swollen that it can hardly keep inside the mouth, and interferes with swallowing. There is an excessive development of the inferior maxillary; the chin is stuck forward, increasing the deformity of the face.

The cranium is very little changed. The anterior posterior diameter is slightly increased. The external occipital protuberance is voluminous. Radioscopic examination shows an irregular thickening of the bones of the cranium, an exaggerated development in height and in depth of the frontal and maxillary sinuses, which explained the prominence of the supraorbital ridges of the cheek bones.

In the upper limbs, while the arms and forearms have a normal volume, the wrists show a certain degree of hypertrophy, but the *hands have characteristic deformities.* They are large, thick and spade shaped. The development is in the thickness and width of the hand and affects both the bones, as shown by X-ray and the soft parts. The hand appears to be padded. The fingers are short,

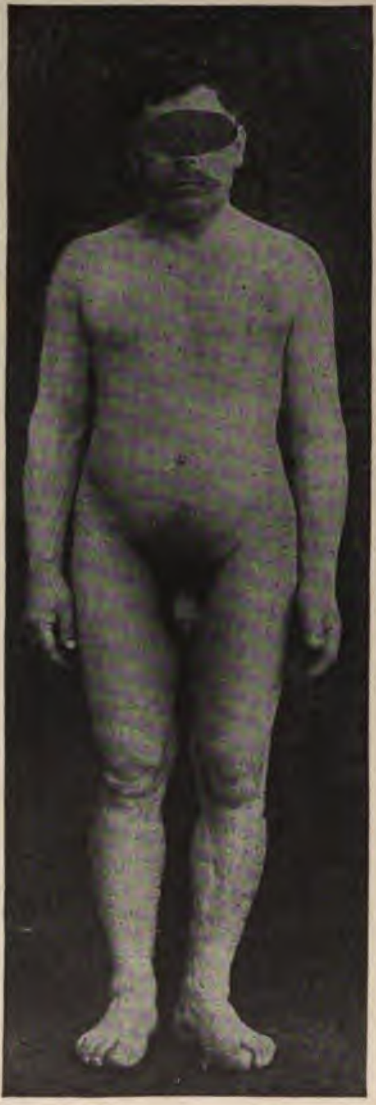


Fig. 7.—Acromegalia (Service of Dr. Lereboullet).

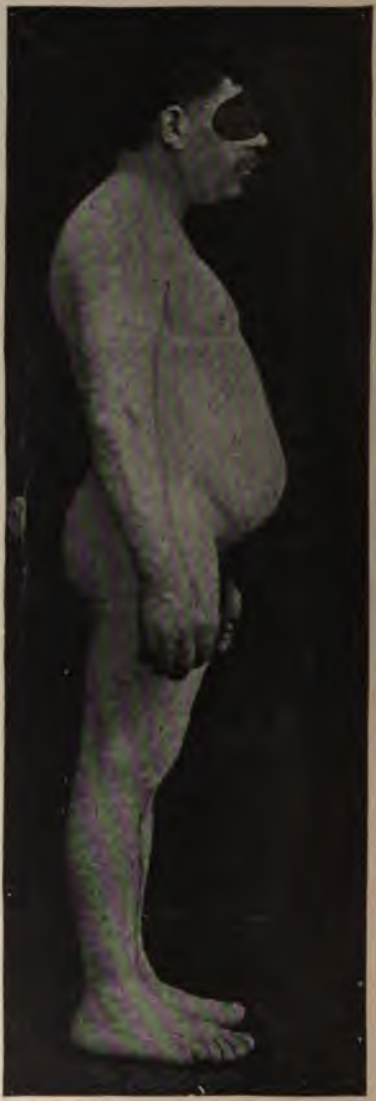


Fig. 8.—Acromegalia (Service of Dr. Lereboullet).

sausage shaped, square at the end and as large at the tips as at the base. The nails are flattened more than enlarged, short and hardly cover the dorsal surface of the last phalange and are striated longitudinally.

The lower extremities show similar deformities. While the thigh and the leg keep their normal size, the ankle and the foot are thickened. The feet in particular, are increased in volume, enlarged and thickened from the heel to the toes.

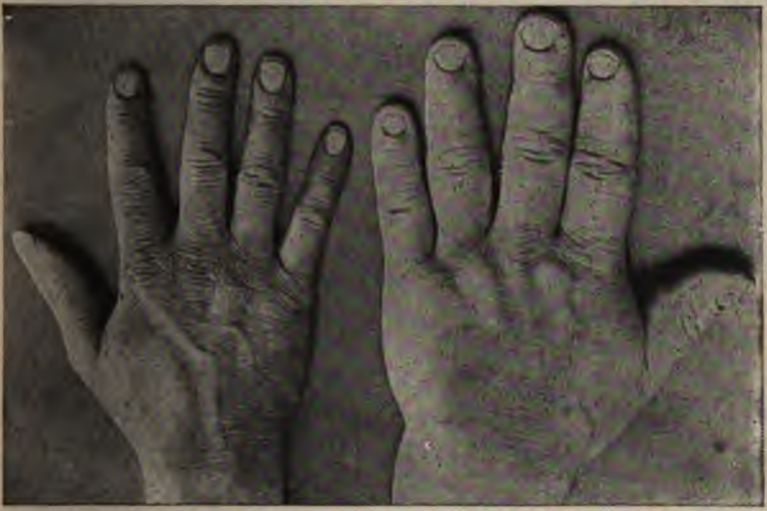


FIG. 9.—Normal hand. (Infroid collection). Acromegalia hand. (Infroid collection).

The malformation of the thorax is less constant. Sometimes these patients show a cervico dorsal kyphosis, so that the head seems to have sunk in the shoulders. The thorax decreases in length, enlarges from front backwards and is separated from the abdomen by a deep groove; protruding forwards and backwards so that there is no question that the original "Punch" must have had acromegalia. This typical aspect of the thorax is due partly to an alteration of the vertebra, by reason of abnormal bone productions and by a hypertrophy of the clavicles, sternum and ribs.

Such are the characteristic dystrophic signs of the disease described by Marie. These patients have a dry, rough skin, often pigmented at the level of the eyelids. The hairs are thick. The articulations are prominent and are often the seat of spasms. Genital disturbances are the rule. In man, frigidity and often atrophy of the testicles.

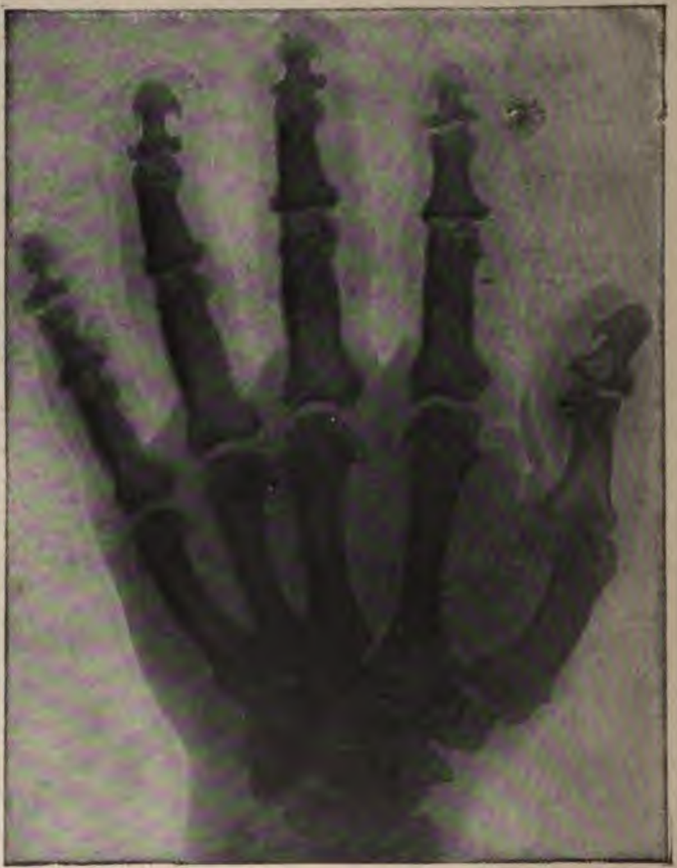


Fig. 10.—X-ray picture of the hand of a case of acromegalia (Infroid collection).

In women the menses decrease or stop altogether. Finally, to this disease is often associated a remarkable splanchnomegalia; the heart is enlarged, without any apparent cause. The liver and spleen are also increased in size.

CLINICAL TYPES.

Certain cases of acromegalia are associated with muscular atrophies (amyatrophic cases), with various neuralgias, intercostal or sciatic (painful cases), when as a result of lesions of the vertebra, the roots are compressed.

There are also mild forms characterized by elongation of the face, proliferation of the inferior maxillary, a slight kyphosis, a more or less noticeable enlargement of the hands and feet, which "is more a condition than a disease." (Chauffard).

EVOLUTION.

Acromegalia usually starts around 25 or 30, very insidiously. In the majority of cases the patients notice that they have to get larger and larger sizes of hats, gloves and shoes, or their friends notice the deformities of the face.

The evolution is usually very slow, but progressive; there are, however, periods of remission. The hypertrophy may remain stationary for several years without interfering with health. The disease may last 20 or 30 years. In other cases, the evolution is much more rapid and the patients die after 3 or 4 years with sign of brain tumor.

ETIOLOGY.

Acromegalia is caused, in the great majority of cases, by a tumor of the pituitary. The gland which normally weighs 0.50 centigrams, can reach a weight anywhere from 3 to 40 grams and become very large. The tumor is nearly always an adenoma, or an adenosarcoma, or a sarcoma; more rarely an epithelioma.

II. GIGANTISM.

The medical disease known under the name of gigantism means an individual whose height is superior to that of others of his species, or his race, and who at the same time shows a certain number of abnormalities, both morphological and functional.

The medical investigation of giants is recent. It followed the description of acromegalia in which Marie definitely differentiated it from gigantism. Brissaud and Maige, then Launois and Roy have shown that very frequently these two conditions occurred together.

GENERAL CHARACTERISTICS OF GIGANTISM.

Giants usually have a height superior to 2 metres. This figure is, however, not absolute. Individuals whose height is between 1.80 and 1.90 metres can be considered as being pathological as regards to the rest of the family.

What characterizes gigantism is not so much the height as the disproportion of the various segments of the body.

Among the giants, some show an excessive elongation of the lower extremities. They appear to be on stilts. This is the macrosketic type described by Manouvrier. Others have extremely long arms in relation to the body. This is the bradysketic type.

While giants are said to have an excessive strength, in reality they are very weak. Their strength, if it does exist, is always temporary and sooner or later these individuals become asthenic, walk around with difficulty and have to be helped.

These subjects have no energy and are both weak in

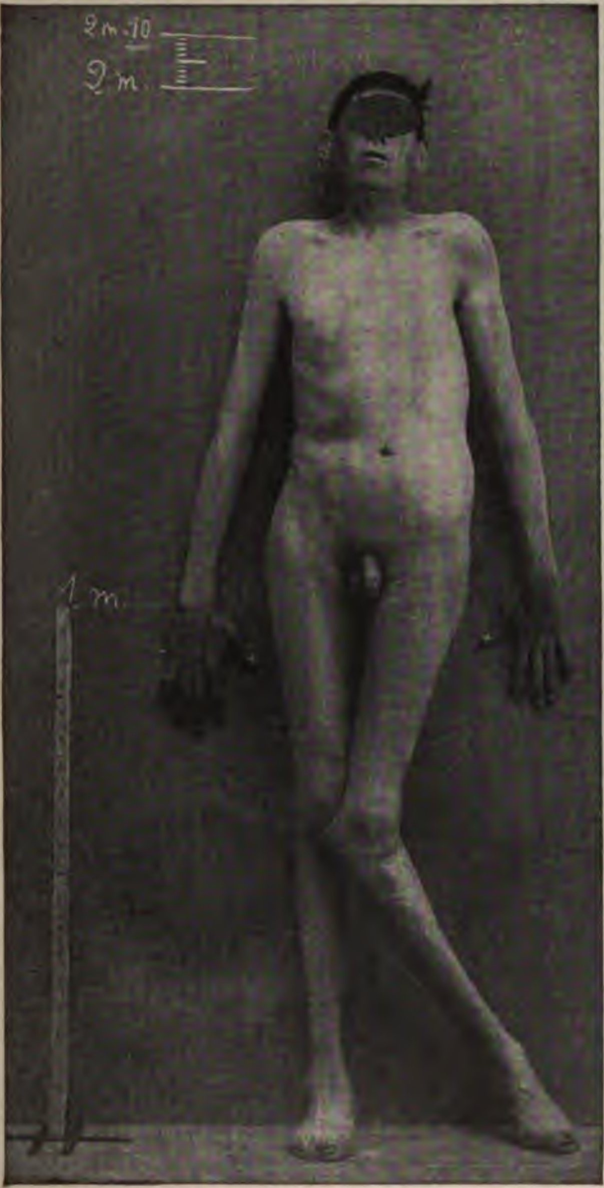


FIG. 11.—Infantile gigantism (Service of Dr. Launois, Infroid collection).

mind and in body. Their mentality is very inferior and they are nearly always impotent and sterile.

CLINICAL FORMS.

Gigantism can be divided into two definite types, between which, however, there are many intermediary forms.

1.—GIGANTISM WITH ACROMEGALIA is characterized by a marked deformity of the spine, so that the inferior portion of the body seems to telescope in the superior segment while the trunk is wider. These individuals resemble anthropoid apes and also show typical signs of acromegalia, the face elongates, the cheek bones are prominent, the nose increases in size, the chin protrudes forward and the hands and legs become enormous. The hypertrophy of the extremities differs slightly from that of typical acromegalia. The fingers have not the sausage shape, for the development is more in length than in width. (Pierre Marie).

2.—INFANTILE GIGANTISM is characterized by elongation of the inferior extremities, accompanied by genu valgum. The head and body extremities remain normal without any deformities.

To these skeletal signs are added signs of infantilism; the genital organs keep the same size they had in childhood. Hairs do not appear as normally; the voice remains frail and childish. Some have even a feminine form; the breast slightly developed, the abdomen rounded, the pelvis broad. Finally, in these giants, the cartilages persist in the adult and the epiphysis do not fuse with the diaphysis.

Even in these cases of infantile gigantism at any time may appear signs of acromegalia. The two types may combine and gigantic infantilism gradually changes to acromegalia gigantism.

3.—GIGANTISM is said to be sometimes found. The exaggerated development of the skeleton in those cases is compatible with good health and good general physique. While the preceding cases were pathological giants, these are normal giants and can be called "hypermetric men."

When, however, these so-called normal giants are examined carefully, they often are found to have a mediocre intelligence. They are more or less impotent, which fact they do not admit and if they live long enough, their physical strength deteriorates very rapidly and deformities of acromegalia will appear.

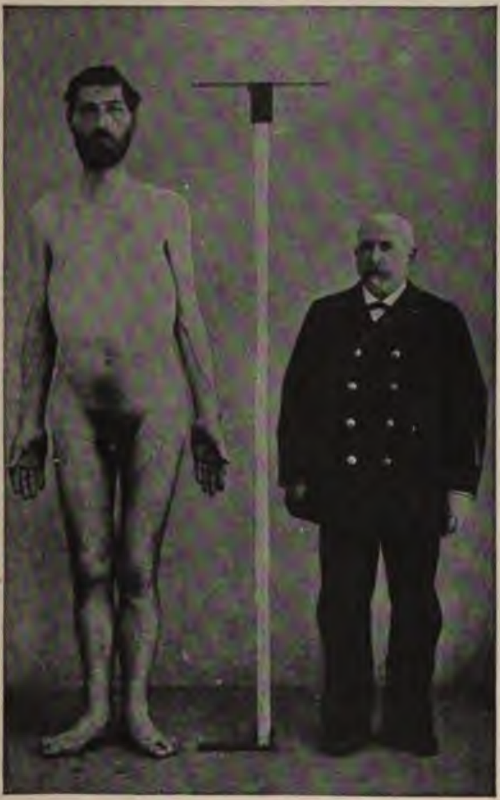


FIG. 12.—Drum major: height 2.12 metres. To the right a man of normal height. (This picture is taken from the book of Drs. Achard and Loeper, collection Infroid).

EVOLUTION.

Gigantism is a disease nearly always found in men. It may begin either at puberty, or earlier in childhood.

Gigantism may stop its evolution at a certain point. It is then called definite. But growth is susceptible to prolongate itself beyond adult life. The gigantism is then called progressive.

The majority of these subjects die young, and rarely live over 40. They emaciate, become cachectic and nearly always end up by developing pulmonary tuberculosis.

ETIOLOGY.

Autopsies on giants, just as in acromegalia, have shown nearly constantly the existence of a tumor of the pituitary. The examination of the skeletons of giants, which have been preserved, in several museums have all shown to Langer an increase in the volume of the sella tursica.

RELATIONSHIP OF GIGANTISM TO ACROMÉGALIA.—Brissaud and Meige then Launois and Roy have maintained that gigantism and acromegalia are two affections having very close connections. Brissaud considers these two dystrophies as one and the same disease, appearing at different ages. Gigantism is acromegalia of adolescence. Acromegalia is the gigantism of adults. Acromegaliagigantism is realized when the exuberance of bones, began in childhood, is continued in adult life.

P. Marie believes that the two diseases, while having certain points of similarity, are independent. Furthermore, the existence of acromegalia in children (Hutinel) seems to refute the theory of Brissaud.

Whatever their relationships, gigantism and acromegalia seem to be due to a hyperplasia and a hyperfunction of the anterior lobe of the pituitary resulting in both cases in a stimulation of the osteogenetic function.

How can we explain that the exaggeration of this function results in these two conditions?

Perhaps by a different evolution of the cellular hyperplasia of the pituitary. When the proliferation follows the normal, gigantism appears; when it is atypical, acromegalia results. In other words, gigantism is due to hyperpituitarism and acromegalia to dyspituitarism.

This conception is still a hypothesis. It has at least the advantage of allowing us to understand how gigantism may be followed by acromegalia or combine with it, when after a period of proliferation, the glandular cells deviate from the normal.

III. PITUITARY INFANTILISM.

This is a fairly uncommon condition, known in France by the observations of Burnier and the investigations of Souques and Chauvet.

It appears at any period of childhood up to 17 and is characterized by an arrest of development. (Children 16 or 20 have a height of 10 or 14) the limbs are thin, while the body has a certain amount of adiposity.

The genital organs, even after puberty, have an infantile aspect. The secondary sexual characteristics are missing: the hairs are few or missing on the pubis and axilla. The beard does not grow. The voice keeps its childish tones. In other words, it gives the complete picture of infantilism.[1]

These patients die from cachexia, after having had symptoms of cerebral tumor or they may succumb to some intercurrent disease, tuberculosis in particular.

---

[1] The abnormal height of castrated individuals is sometimes designated under the name of eunuchoid gigantism. This is not a satisfactory term, as it may be confused with certain pituitary syndromes.

ETIOLOGY.

On autopsy are found various kinds of pituitary tumors; carcinoma, fibroma, teratoma, cysts, etc., or lesions of the pituitary without tumors; tuberculosis, sclerosis, hyperostosis, causing pressure on the pituitary, etc.

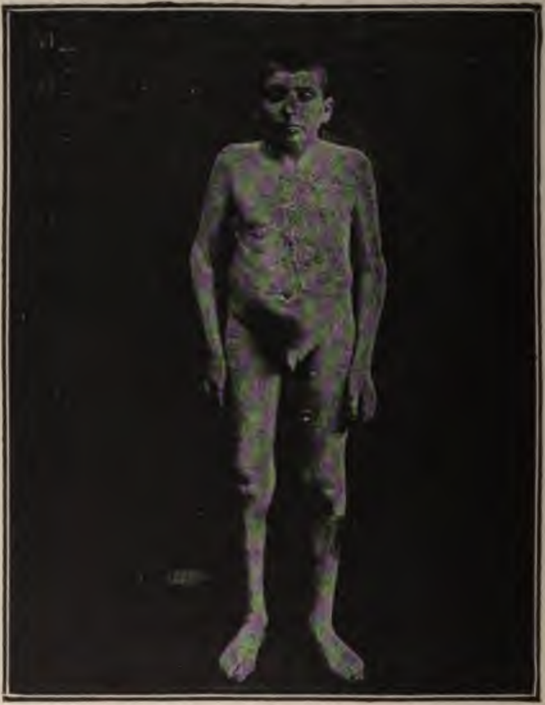


FIG. 13.—Pituitary infantilism (Service of Dr. Souques). This picture is taken from the book of Dr. S. Chauvet: Pituitary Infantilism. A. Maloine et fils. Publishers.

PATHOGENESIS.

Just the opposite of acromegalia and gigantism, which are symptoms of hyperfunction of the gland, it is believed that pituitary infantilism is a syndrome of insufficiency of the anterior lobe or hypopituitarism syndrome. This conception is based on the experimental observations of Caselli, Fichera Aschner, Ascoli and Leguani, who, after removing the pituitary in young dogs, found a complete and immediate stoppage of growth with persistence of the epiphyseal cartilages and an arrest in the development of the genital organs.

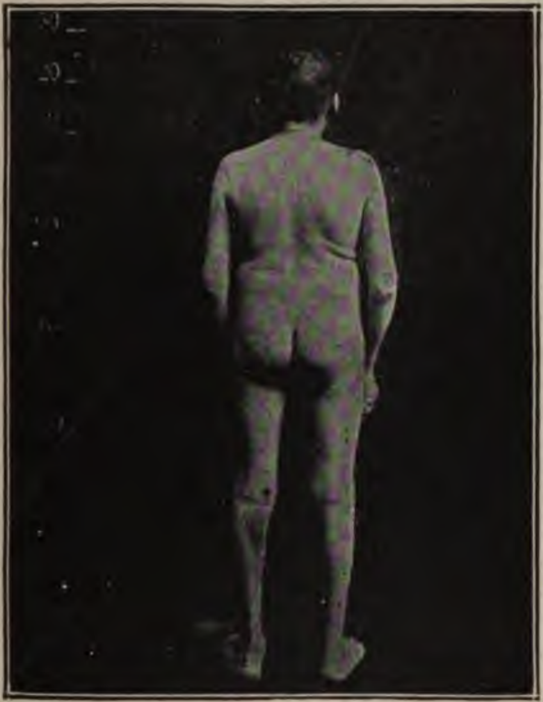


FIG. 14.—Pituitary infantilism. (Same case seen from the back).

IV. ADIPOSO—GENITALIS SYNDROME.

This syndrome, described by Babinski in 1900, then by Fröhlich in 1901 is found either in infancy or in the adult, sometimes even at the menopause.

SYMPTOMS.

It is characterized by two main symptoms: 1.—A marked obesity. 2.—A delay in development or an atrophy of the genitalia.

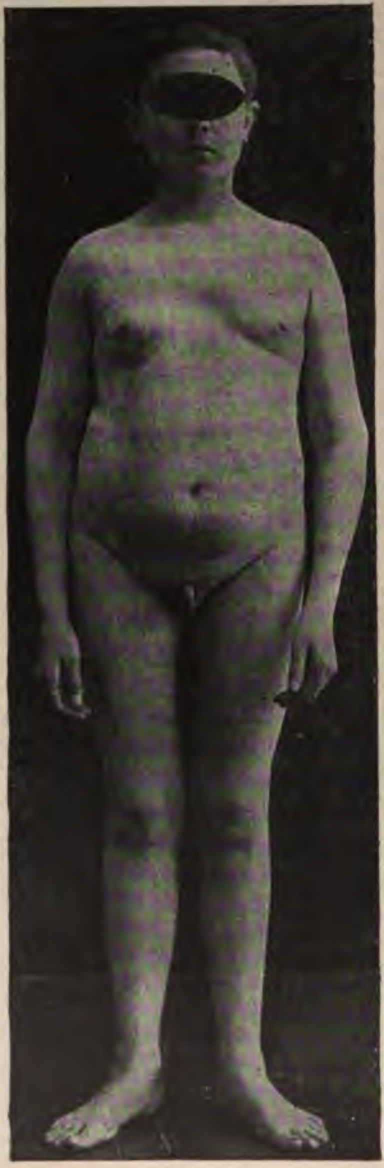


FIG. 15.—Adiposo genitalis syndrome. (Service of Dr. Lereboullet).

1.—OBESITY.—The fat invades the whole body. The face is large and rounded, with a fat neck at its base. In women the breasts are enormous and fall as far down as the abdomen. This hypertrophy consists entirely of fat, for the mammary gland is atrophied and hardly perceptible in the adipose mass. The abdominal walls are relaxed and fall below the pubis and the genital organs, as a sort of an apron. The hips and buttocks sometimes attain enormous proportions. The limbs are transformed in columns ended by pads at the wrists, for these extremities are invaded with fat.

The skin shows a waxy white color; it is hard, dry, cold edematous and not compressible by the fingers. These characteristics resemble very much those of myxedema. Palpation reveals the presence of soft masses in the subcutaneous tissues due to masses of adipose tissue.

The face and hands are

often cyanotic. These patients are dyspneic, due to the fat which infiltrates into the retro peritoneal cellular tissue, the greater omentum mesentery and even the viscera.

The obesity follows a progressive course and can become tremendous. Children of 15 can weigh as much as 50 or 60 kilograms. Adult women sometimes exceed 100 kilograms.

2.—Dystrophia Genitalis.—Genital disturbances, always associated with obesity, vary with the age. In children puberty does not occur. The testicles stay infantile, the secondary sexual characteristics are missing; the hairs do not appear; the voice stays high pitched. In women, the menses become irregular and finally disappear. In man, frigidity and impotence are the rule.

ETIOLOGY.

The adiposo genitalis syndrome has many causes. [1]

In certain cases pituitary tumors have been noticed; in others, tumors at a distance from the pituitary; in others, a serious meningitis or hydrocephalus compressing the gland.

The syndrome may appear following a traumatism; in the classical observation of Madelung a girl of six received a rifle bullet wound in the head. During the following years appeared a marked obesity. At 9 years of age she weighed 42 kilograms. Exceptionally luetic or tuberculous lesions of the pituitary are to blame.

PATHOGENESIS.

Since the observation of Fröhlich, it is believed that the syndrome of adiposo-genitalis is the result of disturbances of function of the pituitary.

---

[1] Clinically these individuals present evidence of thyroid and ovarian deficiency. Lack of ovarian stimulation is noticed in the relative or absolute amenorrhœa and sterility, primary or secondary. Thyroid deficiency is noted by symptoms approaching more or less closely the picture of myxedema.

The most reasonable theory is that suggested by Fischer, Erdheim and Cushing. While acromegalia is due to a hyperfunction of the anterior lobe, pituitary infantilism must be due to hypofunction of this lobe. The syndrome of adiposo genitalis seems to be due to a lesion of the posterior lobe. When it is the result of a pituitary tumor, the latter is developed towards the base of the brain more than towards the base of the skull. In the cases in which at autopsy the pituitary is found normal, both from a macroscopic and microscopic point of view, and in which a tumor is noticed at some distance from the gland (tumor of the dura mater, of the cerebellum, etc.) or a chronic hydrocephalus, there is compression, more or less distinct, of the posterior lobe and the floor of the third ventricle.

Acromegalia can be associated with a syndrome of adiposogenitalis, when a tumor of the anterior lobe compresses or invades the posterior lobe.

V. PITUITARY GLYCOSURIA.

Clinical observations and experimental studies have established the existence of pituitary glycosuria.

It was first noticed by Loeb in 1884 during the course of pituitary tumors. P. Marie in 1886 found it present in about one-half the cases of acromegalia. Launois and Roy also noticed it in giants. It is also found in pituitary infantilism. It is not present in the syndrome of adiposogenitalis; in fact, quite a few cases have an increased tolerance for sugar.

Its clinical characteristics are very variable. The glycosuria may be continuous or intermittent. It may disappear under the influence of diabetic treatment. The quantity excreted is sometimes quite large and can reach more than 1000 grams daily. It is often associated with other diabetic symptoms: polyphagia, polyuria and is complicated by acidoses.

Its pathological mechanism is still very much unknown.

1.—GLANDULAR ORIGIN.—There is a pituitary glycosuria, just as there is a pancreatic glycosuria or an adrenal or thyroid glycosuria. The posterior lobe is the only one which enters in this mechanism; the anterior lobe is inactive. The question comes up whether we are dealing with a hypo or hyperactivity of the gland.

It can be interpreted as hyperfunction if we base ourselves on the experimental observations of Borchardt, who caused a glycosuria by injecting in rabbits, extracts of the posterior lobe. Does, however, this glycosuria occur directly or through the intermediary of the pancreas or the liver? Claude and Baudion having found that the injection of the extract of the posterior lobe only brought on a glycosuria in man after the ingestion of glucose, believe that pituitary glycosuria is an alimentary glycosuria, brought about by hepatic insufficiency. H. Cushing has given a different conception of the mechanism of glycosuria. After having experimentally removed an important part of the posterior lobe, he found in animals at first a period of glycosuria, which is followed by a second period in which the tolerance to glucose is increased and obesity sets in. During the second period, the injection in this animal of the extract of the posterior lobe causes again a decrease in the tolerance and re-appearance of the glycosuria. According to Cushing, the product of the secretions of the posterior lobe goes through the third ventricle in the cerebro spinal fluid and from there into the general circulation. Any encephalic compression, resulting in a stagnation of cerebro spinal fluid, causes at the same time an insufficiency of the posterior lobe.

2.—NERVOUS THEORY ORIGIN.—According to this the glycosuria is due to an irritation or a lesion of the base of the brain. At the level of the pituitary, there is a centre which regulates glycogenesis; there is also one in the bulb and in other portions of the brain. The frequency of glycosuria in cerebral hemorrhages or meningitis is well known, as is also the case in brain tumors.

Aschner believes that the glycosuria is due to a lesion at the base of the third ventricle at the level of the tubercinereum.

Camus and Roussy, think that so-called pituitary glycosuria is due to the irritation of regulating cerebral centres located in the inter peduncular gray matter.

VI. PITUITARY POLYURIA.

As in the case of glycosuria, polyuria has been noted in the course of acromegalia, infantilism. In Fröhlich's syndrome it is sometimes found without glycosuria. It has occurred after traumatic lesions of the pituitary (Frank); it may be caused by a solitary tubercle (Haushalter and Lucien) or by a secondary carcinoma (Simmonds).

Clinically, this polyuria is very variable. It may vary from 2 to 8 liters daily. The quantity varies from day to day. The diuresis which follows the ingestion of liquids is slower than in normal individuals. For this reason, the quantity of urine secreted during the night is more abundant than normal (Berge and Schulmann). There is not always any relationship between ingestion of liquids and the amount of urine excreted. The polyuria is not necessarily accompanied by polydipsia and the excretion can be superior to the absorption. In other words, the pituitary polyuria consists essentially in a disturbance in the mechanism regulating the water and the exaggeration of its elimination.

Its pathogenesis is as indefinite as that of glycosuria. Some consider it as an indication of insufficiency of the posterior lobe, for the injection of extracts of the posterior lobe causes a decrease in the diuresis. Others doubt the pathogenesis of the pituitary. Cushing has shown that a simple manipulation of the posterior lobe or the puncture of this lobe in the infundibulum in animals causes polyuria. Camus and Roussy produced it in animals by irritating the nerve tissue in the neighborhood of the pituitary, without touching the gland itself. According to these writers, there is in the region of the infundibulum or of the tuber cinereum, a center regulating the amount of water in the organism, the irritation of which causes polyuria.

It appears, therefore, as if polyuria was a sign of a lesion of the pituitary or of the neighboring tissues.

PITUITARY SYNDROMES AND TUMORS OF THE PITUITARY.

All tumors of the pituitary do not necessarily produce a pituitary syndrome. A tumor of this gland can remain latent or only manifest itself by symptoms of hypertension or compression.

In the large majority of cases, the syndromes of pituitary disease which we have just described, are associated with the presence of a tumor. We have seen that acromegalia, except in a very few cases, is due to a pituitary tumor. The same holds true of gigantism. Pituitary infantilism, the syndrome of adiposo-genitalis, the glycosuria, the polyuria, can also be symptomatic of a tumor in the region of the pituitary compressing the gland itself or its infundibulum.

For this reason, whenever one of the previously described syndromes are present, a tumor of the pituitary should be suspected.

CLINICAL SIGNS OF TUMORS OF THE PITUITARY.

1.—Symptoms of Cranial Hypertension are present in the majority of cases: severe headache, diffuse or localized, frontal, retro orbital or bitemporal, with pain or pressure over the eyes, when the headache is due to a distension of the glandular capsule. Various neuralgias; ocular, facial, or occipital; vertigo and vomiting of the cerebral type.

Certain symptoms seem peculiar to pituitary tumors. They are: low body temperature; it may go down to 34 or 33 centigrade and seems to have some relationship with the neighborhood of the gland to the thermic centres; sleepiness; some patients have narcoleptic spells or become torpid or indifferent; psychic disturbances are very frequent, mystic delirium, persecution, depressive mania, etc.[1] A certain number of insane in the past were termed: *amaurotic insane*.

2.—Ocular Symptoms are those which we have known for the longest time; they are the most common, the most constant and the most important for the diagnosis of tumors of the pituitary or its neighborhood. They are explained by the close relationship between the pituitary and the optic tract. The latter can be injured at the level of its three segments: pre-chiasmic, chiasmic and retro-chiasmic.

(*a*) A pre-chiasmic lesion results in visual disturbances in the corresponding eye: narrowing of the visual field, amblyopia, then amaurosis. According to the nature of the tumor the amaurosis may come on rapidly or at the end of several years.

(*b*) A chiasmic lesion suppresses vision on the nasal side of both retina. It results in a bilateral hemianopsia, a frequent symptom of great diagnostic importance and which often precedes amaurosis. The visual disturbance at first may only be for colors and is a hemidyschromatopsia. The hemiopic reaction of Wernicke; that is, the absence of the pupillary reflex to light in that part corresponding to the visual field, is also an important symptom, but difficult to bring out.

---

[1] It is believed that some of the unpleasant symptoms of the menopause are due to pituitary disturbance—probably a hypersecretion relative to the secretion of the thyroid and ovary which are undergoing more rapid retrogression.

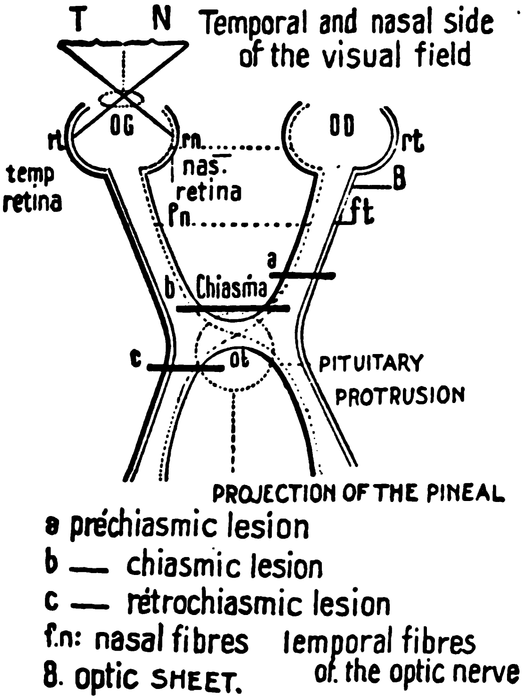


FIG. 16.

More rarely the hemianopsia is temporal, unilateral, when the other eye is already amaurotic.

(c) A retro-chiasmic lesion causes a bilateral homonymous hemianopsia. Lesions in the fundi are nearly as frequent as modifications of the visual field.

Edema of the disk is not as frequent as in other forms of brain tumor. Optic atrophy, by direct compression, is more often met with. Ocular paralysis is exceptional.

Quite often these ocular disturbances are overlooked, even by the patients. A certain number of pituitary syndromes have only very slight ocular symptoms: hemianopsia should be carefully looked for, as well as a careful examination of the fundus of the eye, even in the absence of any subjective symptom, when a pituitary tumor is suspected.

3.—Radiological Examination.—Oppenheim, Beclere and Jeaugeas, Toupet and Infroit have insisted on the special interest of radiography of the sella tursica and give the technique to follow: the sella tursica must be oriented to an absolutely parallel plane to the plate, and the normal ray must pass perpendicular through the centre of the body excavation, so that the two clinoid apophyses (anterior and posterior) be superimposed; the outline of the sella tursica seen in profile, is indicated on the plate by a definite line.

X-ray does not give definite findings when the tumor develops right away towards the brain: in those cases all that is noticed is an enlargement of the superior opening of the sella tursica which is very difficult to appreciate. More often, however, the tumor wears out and destroys the bony covering; the posterior clinoid apophyses are altered; the outline of the sella becomes irregular. If the tumor develops forward, which is most frequently the case, the sella tursica shows at the level of its pommel, an excavation, very easy to see. The normal sella tursica of an adult has an anterio posterior diameter of about 10 to 12 millimeters and has a depth of about 8 centimeters.

Cushing recommends taking X-ray pictures of the patients with the head bent slightly forward, so as to appreciate the depth of the sella tursica. By means of

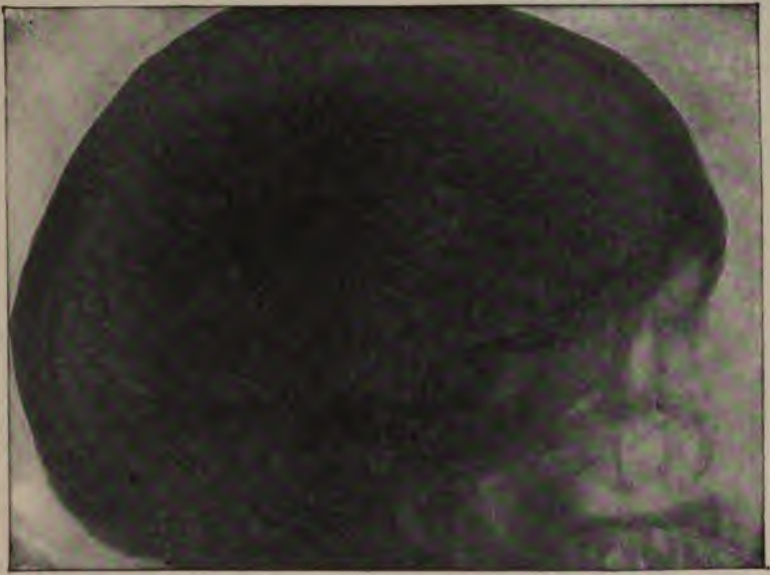


FIG. 17.—Normal sella turcica (Infroid collection).

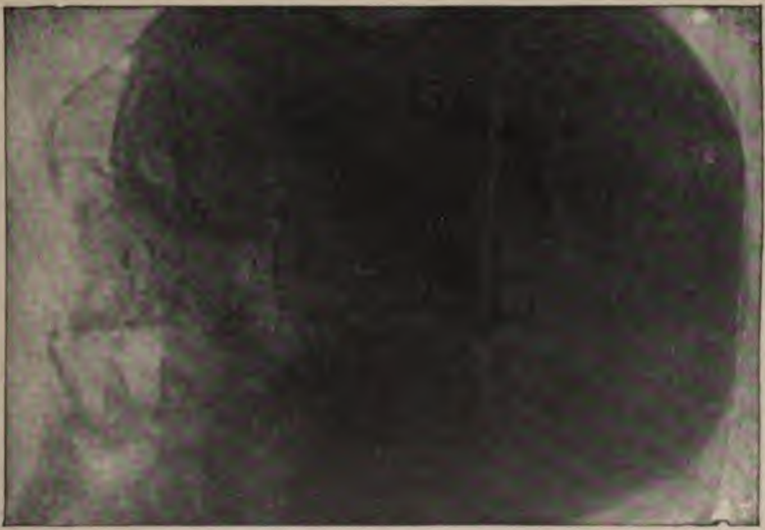


FIG. 18.—Rounded and deformed sella turcica due to a pituitary tumor (Infroid collection).

successive pictures, it is then possible to follow the evolution of the tumor.

In certain cases the X-ray allows us to find in the pituitary fossa, or in the adjacent region, abnormal shadows which are indications of partial calcification of the tumor.

ABORTIVE PITUITARY SYNDROMES.

1.—AT PUBERTY are sometimes observed disturbances of growth characterized by elongation of the limbs, or enlargement of the extremities. These disturbances, associated with a delay in the development of the genital organs, is a mild pituitary syndrome.

Brissaud has found in adolescent symptoms of transitory acromegalia: large hands, big feet, large nose, deep voice, which become less marked as growth continues.

Launois and Roy have also noticed at puberty a transitory gigantism characterized by a lack of harmony between the growth of the trunk and of the lower limbs. The children appear to be on stilts and often have genu valgum. The disproportion of the limbs disappears when the development of the genitals is complete. This dystrophic condition is also found in young girls whose height is excessive, with very long legs, while the thorax stays narrow and the breasts are hardly developed. Menstruation is irregular or accompanied by waves of heat and headache.

In other young girls the syndrome of adiposo-genitalis is just noticeable around puberty. The body keeps the rounded appearance of the child; the skin is white, edematous, possibly myxedematous. The mons veneris is infiltrated with fat; the hairs are scarce and the menses few, irregular and painful.

2.—DURING PREGNANCY the anterior lobe of the pituitary shows histological modifications and the gland hypertrophies. During the course of pregnancy, symptoms of acromegalia are sometimes observed; thickening of the soft parts of the nose, of the lips; increase in the volume of the fingers, which go back to normal after delivery. Certain cases of glycosuria during pregnancy can be the only indicative signs of a hyperfunction of the gland.

3.—At the Menopause sometimes similar symptoms are noticed. Acromegalia has been noticed after the removal of the ovaries (Goldstein), after the sudden stoppage of the menses (Briquet). Certain cases of adiposity of the menopause are due without a doubt to pituitary insufficiency, just as much as to ovarian insufficiency.

PITUITARY SYNDROMES IN INFECTIONS.

Renon and A. Delille believe that certain infections, such as, typhoid, pneumonia, etc., in which the arterial blood pressure is decreased and the pulse accelerated, are due to a pituitary hypofunction. Pituitary organo therapy when used in the infectious diseases increases the arterial pressure, decreases the tachycardia, increases diuresis and causes the re-appearance of sleep and appetite. It is well to remember that these same diseases cause similar symptoms of cardio vascular asthenia by means of adrenal insufficiency.

TREATMENT OF PITUITARY SYNDROMES.

Three types of treatment have been used in the various pituitary syndromes.

1.—Organo Therapy.—The preparations used are either the total extract of both lobes, or the extract of the posterior lobe, which is the only one that has any physiological action, or are aqueous extracts known under the name of pituitrin. The average doses vary from 0.10 to 0.40 centigrams daily (the last mentioned dose corresponding to about one-half of the gland of an ox). In acromegalia, organo therapy often does not give any results; its use, furthermore, seems illogical in an affection which is probably due to a hyperfunction of the gland. Some writers, however, claim that they have been able to get a decrease in the headache; others have found an increase in the disturbances and even real osteogenetic stimulation. If, therefore, pituitary extract is used in gigantism of acromegalia, it should be done very cautiously.

It seems to give variable results in adiposo genitalis and in infantilism. When these syndromes are caused by a tumor of the gland, the action of organo therapy is, of course, valueless. When, however, inflammatory lesions are the cause, then organo therapy often is very beneficial. Lereboullet recommends giving a combination of pituitrin with very small doses of thyroid. Etiological treatment can, and should, be instituted, if there is the possibility of a luetic affection.

The two most definite indications of organo therapy are pituitary polyuria and infectious diseases.

(*a*) *Pituitary Polyuria.*—A certain number of observers have established beyond doubt the anti-diuretic action of pituitary extract. Oral medication by means of the extract is inefficient, but the subcutaneous injection of the extract of the posterior lobe (equivalent to one-half the posterior lobe of an ox) causes an immediate improvement. On the same day the quantity of urine excreted will be reduced one-half and in a few days brought back to normal. The action is only temporary and rarely lasts more than twenty-four hours. Polyuria re-appears as soon as organo therapy is discontinued (Lereboullet and Faure-Beaulieu). This therapeutic action can only be obtained by sufficiently active medication.

(*b*) *Infectious Diseases.*—Renon and A. Delille have studied the use of organo therapy in infectious diseases; in particular, in severe typhoid associated with myocarditis. In the majority of cases, the medication caused a rapid rise in the blood pressure, a decrease in the tachycardia and an increase in the diuresis.

2.—RADIOTHERAPY.—It has been studied in France by Beclere and Jaugeas in cases of acromegalia and gigantism. In some cases treatment by the fronto temporal route has given satisfactory results, which are worth describing: arrest of growth of the extremities—without, however, any regression—the re-appearance of the genital functions and particularly, improvement of the visual disturbances, depending of course on the treatment having been started early enough, before optic atrophy.

This treatment may be attempted in the syndromes due to a diagnosed pituitary tumor.

3.—SURGICAL TREATMENT.—Theoretically, this is the best treatment in tumors of the pituitary. The removal of the pituitary by the nasal route has given good results, in spite of a high mortality. It is, however, only applicable to those tumors which grow in the direction of the sphenoidal sinus.

In acromegalia in which the tumor surely is located in the sella tursica, intervention has the greatest chance of being successful. In certain cases there has been a decrease of the signs of compression and even a regression of the dystrophic disturbances (Toupet).

In the adiposo-genitalis syndrome, the operative conditions are not as satisfactory, for the variability of the location of the lesions makes the detection of the tumor and its removal very problematic. There are, however, certain cases of simple adiposo-genitalis syndrome or associated with acromegalia in which the symptoms have retrograded after the removal of the pituitary tumor which had only compressed and not destroyed the centres. Cysts and parapituitary tumors of the dura mater have naturally a less favorable operative prognosis than tumors of the anterior lobe. Whatever the syndrome, the posterior lobe and the infundibulum must not be removed.

4.—Symptomatic Treatment.—This is unfortunately the only thing to do in the majority of cases. Cranial decompression is often the only therapeutic resource to relieve the patients from pains, headache, neuralgias which are very intensive and resist the usual symptomatic medications.

CHAPTER IX.

PATHOLOGY OF THE PINEAL GLAND.

Up to the last few years the pineal gland was considered by anatomists to be "a degenerated gland with only rudimentary functions or none at all" (Testut), representing, from a morphological point of view, the pineal eye of lower animals. He mentioned out of curiosity that Descarte considered this gland to be the centre of the soul and Magendie believed that it regulated the circulation of cerebro spinal fluid.

This conception has been modified by the anatomical and clinical study of tumors of the pineal. A certain number of observations have established the fact that these tumors cause not only symptoms of nerve compression and cranial hypertension, but they also give rise to a syndrome which is characteristic, and which consists in an exaggeration of growth, sexual precocity and sometimes abnormal psychosis.

It seems, therefore, to be well established that the pineal plays a part in the physical and sexual development, and from this point of view can be considered as a gland of internal secretion.

PINEAL SYNDROME.

It was first studied in 1908 in the investigations of tumors of the pineal gland by Marburg and by Frankl-Hochwart. Observations by French writers are still more numerous: those of Raymond and Claude, Apert and Porak being the most important.

Pineal tumors are usually met with in male children, at least 12 years of age.

SYMPTOMS.

These are of two different kinds:

1.—Dystrophic symptoms.

2.—Symptoms of cerebral tumors.

I. DYSTROPHIC SYMPTOMS.

A rapid increase in growth, together with an increase in size of the genitalia, and the appearance of hairs in the axilla, face and pubis are the chief elements of pineal syndromes and have been called by Pellizzi, *Precocious macrogenitosomia.*

1.—Height increases rapidly and is much more than that of the average child of that age. This progression shows an important characteristic. There is no deformity or disproportion of any segment of the body. X-ray of the bones shows that the size of the cartilages are reduced in relation to the age of the patient. In other words, growth is accelerated, but follows the normal course.

2.—The Genital Organs become excessive. The testicles and particularly the penis increase excessively in size. At 8 or 10 years of age, these children have erections and ejaculations containing spermatozoa.

3.—The Hairs appear precociously on the pubis, the axilla and the face. The change in the voice has been observed in children of 3 or 5. This syndrome may not be present as a whole. Some patients have an excessive growth, a marked proliferation of hairs and the genitalia stay small; others have an excessive genital development, while the hairs are not developed. A psychic hyperactivity, characterized by an astounding intellectual precociousness has been noticed in some cases, parallel to the sexual and physical development.

To the signs of macrogenito-somatisms are superimposed certain observations of adiposity and diabetes insipidus with analogous characteristics to those observed in pituitary syndromes.

II. SYMPTOMS OF CEREBRAL TUMORS.

They are explained by the close relationship between the pineal and the neighboring nerve structures.

This gland is located between the two anterior tubercula quadragemina, the posterior portion of the third ventricle, on top of the aqueduct of Sylvius, and below the corpus callosum from which it is separated by the velum interpositum, which contains the veins of Galen.

A tumor of the pineal gland can sometimes compress the aqueduct of Sylvius which connects the third and fourth ventricle, or the veins of Galen, disturb the cerebrospinal circulation and cause a marked hydrocephalus.

If we remember that the anterior tubercula quadragemina are in relation with the optic centers and that posteriorly the auditory centers are below them, the gray matter surrounding the aqueduct of Sylvius contains the nuclei of the nerves of the eye (3rd pair in particular), it is easy to see how tumors of the pineal can cause auditory or visual disturbances.

These patients have a constant headache, very painful and varying in location. (Frontal, occipital or temporal) and cerebral type of vomiting, with stupor, torpor, or narcolepsia, as the symptoms of intra cranial pressure increase.

Hydrocephalus is the rule in children below 10 and causes a separation of the cranial sutures appreciable by palpation or X-ray.

The ocular disturbances are particularly characteristic. In the cases coming early under observation: inequality of the pupils, sluggish reaction of the pupils, a bitemporal hemi-anopsia or blindness depending on the lesions of the tubercula quadragemina being united or bilateral. Sometimes, when the hydrocephalus is very marked, congestion then atrophy of the optic disk are the only symptoms. Ocular paralysis in the parts supplied by the oculo motor nerve (strabismus, diplopia) can be early symptoms.

Auditory disturbances are also met with: they consist of buzzing, or whistling sounds. After a time: bilateral, but unequal deafness, is the rule.

Finally, when the symptoms of hydrocephalus grow rapidly worse, signs of cerebellar compression are noticed: vertigo, nystagmus, tremors, asynergy, or paralytic, unilateral or bilateral phenomena.

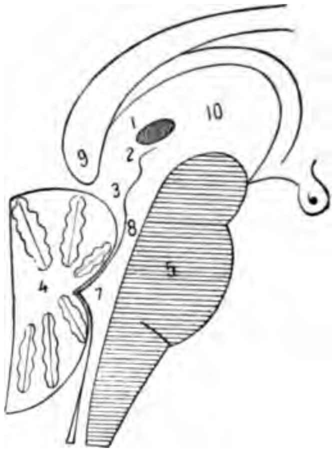


FIG. 19.—Diagram of the relationship of the pineal body to other structures. (According to Testnut). 1. Pineal body. 2 and 3. Anterior and posterior corpora quadrigemina. 4. Cerebellum. 5. Pons. 6. Pituitary. 7. 4th ventricle. 8 Aqueduct of Sylvius. 9. Corpus callosum. 10. Lateral wall of 3rd ventricle.

In certain tumors, (teratoma) which contain cartilagenous tissue or calcarious deposits, the radiological examination will reveal abnormal shadows in the region above the sella tursica.

EVOLUTION.

Tumors of the pineal gland usually start with symptoms of intracranial pressure and hydrocephalus; for instance the headache, the vomiting, the visual disorders are the first signs to attract attention. The dystrophic changes occur after a time and allows us to localize the tumor. In certain cases, the rapid increase in height and the appearance of diabetes insipidus h been the first symptoms.

The duration varies from 3 to 18 months with some remissions. Death is the end. It may occur during an epileptiform attack or from an intercurrent pulmonary affection, or the patients become slowly cachectic and die in coma.

DIAGNOSIS.

The preceding symptomatology is very characteristic, but it may be missing.

Certain pineal tumors are very slow. Others take on the appearance of a tuberculous meningitis. Others finally are manifested by a hydrocephalus syndrome or compression and give the appearance of an ordinary brain tumor without any dystrophic manifestations.

We will only discuss the diagnosis of complete syndromes in which pineal disturbance is very definite.

The increase in the height, the precocious appearance of the secondary sexual characteristics, obesity are symptoms which may belong to other glandular syndromes, the pituitary in particular.

Gigantism differs from the pineal syndrome: 1.—Abnormal growth (lack of proportion); 2.—Atrophy of the genital organs.

Fröhlich's Syndrome is characterized by obesity, but there is a genital atrophy.

Adrenal Virilism resembles the pineal syndrome, due to the obesity and the precocious appearance of the secondary sexual characteristics. It is, however, more frequent in women. The height remains stationary; there is a hyperasthenia and a remarkable hypertrichosis and finally while evidences of cerebral tumor are absent, palpation reveals the existence of tumor in the region of the kidney.

PATHOLOGICAL ANATOMY.

The chief lesion consists in a marked internal hydrocephalus, dilatation of the third and lateral ventricles, compression of the floor of the third ventricle (even the pituitary) and the cerebral hemispheres.

It is usually inside of the third ventricle that the pineal tumor is found. It is sometimes the size of a small nut or a small apple. More rarely it develops posteriorly towards the cerebellum. The tubercula quadragemina are then compressed or destroyed; the veins of Galen are dilated and filled with blood. The aqueduct of Sylvius is compressed or obliterated. Some large tumors destroy the roof of the aqueduct, the posterior part of the corpus callosum and the posterior portion of the optic layers.

The histological structure of these tumors is variable. Those most often met with are cysts, then teratoma. Glioma, sarcoma and carcinoma. Mixed tumors have also been found and occasionally tubercles.

PATHOGENESIS.

We still have much to learn about this gland, both from a histological and physiological point of view.

Histologists do not agree on its structure. Some only recognize nerve cells, others derivatives of nerve and glandular cells, the latter characterized by large nuclei, sometimes dark, sometimes light, and with a granular or vascular protoplasma.

One fact seems to be established; that is, that the gland only appears active in childhood, and from the age of 7 on it seems to involute, which fact manifests itself by cysts and calcarious deposits. From these histological modifications it can be understood why tumors of the pineal gland only develop in infancy.

Marburg thinks that he has been able to find in the somaric disturbances of pineal tumors various disturbances of the pineal secretion. He believes that the exaggerated growth and precocity are due to hypopinealism, obesity to hyperpinealism and cachexia to apinealism. This conception is manifestly insufficient to explain all the facts, but the conception of Marburg has been the starting point of experimental investigations. Berkeley has noticed in young animals fed pineal gland, an evident action on the physical development. Cornell and Goddard have obtained in backward children after pineal organo therapy, a stimulation of the intellectual development. Biach and Hulles, on examining the pineal gland of animals which had been castrated early, have found an atrophy of the gland. Harroax, having obtained a complete removal of the pineal gland in guinea pigs and rats, has found a precocious development of the sexual glands.

All these observations should be confirmed. There seems, however, to be some relationship between the pineal and the genital apparatus. At the present time, it is impossible to say if the syndrome of macrogenitosomia is due to hypo or hyperfunction of the pineal gland, for in certain cases the development is contradictory. The hairs are well developed, but the penis and testicles are atrophic. In certain cases, the pineal has been found compressed, and the question comes up if we are not dealing with complex pluri-glandular modifications.

TREATMENT.

There is no treatment except the alleviation of the symptoms. Sooner or later the signs of intracranial hypertension predominate. The patients are nearly always improved by lumbar puncture if the aqueduct of Sylvius is not compressed. Ventricular puncture or decompressive craniotomy are the only therapeutic procedures which will help the patient.

CHAPTER X.

PATHOLOGY OF THE TESTICLES.

FUNCTIONS OF THE TESTICLES.

In 1889 Brown-Sequard maintained, before the Biological Society, that the internal secretion of the testicle keeps up physical and sexual strength. When these decrease, under the influence of age or disease, they can be stimulated by means of injections of the extracts. These ideas had an immediate application: the introduction of testicular extract in therapeutics, and an enormous variety of conditions were treated by this medication. The results, however, did not come up to the expectations and the theory of Brown-Sequard as regards the testicular extract was abandoned.

To-day, the testicle is considered as having a double secretion: an external or seminal secretion, resulting in the elaboration of the cells of reproduction; the spermatozoa and an internal secretion controlling the evolution of the sex. The histological investigations of Ancel, Bouin and Loisel have enabled us to differentiate in the testicle two different types of glands corresponding to these two secretions. The seminal glands are made up of the seminiferous tubules. The interstitial gland or the gland of morphogenesis is represented by more or less voluminous islands of large cells between the seminiferous tubules and in the neighborhood of the blood vessels. These cells have a glandular appearance. They contain secretions: fats, crystals, granules, pigments, brought out by various histological and chemical reactions and soluble toxic materials, albuminoid in composition, which have been demonstrated by physiological experimentation.

THE INTERSTITIAL GLAND OF THE TESTICLE HAS A DOUBLE FUNCTION.

1.—It maintains the nutrition of the seminiferous tubules and protects the spermatic cells by fixing or neutralizing the toxins which are liable to affect them. This action is more or less hypothetical and the mechanism has not been sufficiently demonstrated.

2.—It controls the whole of the sexual characteristics. This is its most important action and has been demonstrated by physiology, histology and experimentation.

We must remember that the sexual characteristics in the young, as well as in the old, consist of:

a.—The primary characteristics, namely, the sex itself.

b.—The secondary sexual characteristics: the growth of the genital tract and its adnexa.

c.—The tertiary characteristics: the development of the skeleton and the sexual instinct.

The decrease, then the disappearance of the sexual instinct in old men, as well as in old animals, corresponds to a physiological evolution of the interstitial gland; the cells lose their fatty granulations, their crystals, and atrophy.

The study of the cryptorchidism in animals shows clearly the action of this gland. Certain animals with cryptorchidism have well developed external genitalia, and have all the characteristics of a stallion except that they cannot reproduce, while others resemble castrated animals. In the first type of case, the interstitial gland is preserved while it is missing in the other. The ligation of the vas deferens when performed on young animals does not modify their development and does not prevent the appearance of the sexual characteristics. Richon and Jeandelize, Tournade, Bouin and Ancel have noticed that this ligation is followed after a few months by an atrophy of the seminal tubules, while the interstitial cells remain normal. Similar observations have been made by Bouin and Ancel following the injection of zinc chloride in the head of the epididymis and in man after gonorrheal or tuberculous epididymitis.

The exposure of the testicle to the X-rays causes the disappearance of the seminal cells, but does not affect the interstitial ones (Bergonie, Tribondeau, Villemin and Regaud). These animals retain their genital attributes and instincts. They cannot reproduce, but are not impotent.

Inversely, the destruction of the interstitial gland, which has been accomplished by Ancel and Boiun in young rabbits, after ligation of the spermatic artery and venous plexus, caused an arrest of development of the sexual characteristics.

It is the study of castration in animals which gives the most important demonstration of the action of the testicular internal secretion on growth and the development of the sexual characteristics.

Animals castrated when they are young, before they have acquired their definite form, have an arrested development. The distinct characteristics of the male sex do not appear. The subject develops an exterior appearance which resembles the female. The features stay refined and the body is less developed.

The skeleton shows a notable elongation: castrated animals are larger than the controls. The growth is chiefly of the posterior limbs and is due to the persistence of cartilage beyond the normal period.

The external genitalia show a more or less important arrest of development, depending on the species, but it is always noticeable. The experiments on dogs by Guyon, Legneu and Albarran have shown that castration is followed by an atrophy of the seminal vesicles and prostate.

Important changes also occur in the skin. The skin is delicate, the hairs are softer and not as numerous. The feathers of the capon differ from that of the rooster: the feathers of the tail remain horizontal instead of rising upwards.

The attributes of the sex are modified: in the young castrated rooster the comb and the spurs are rudimentary or do not develop.

The voice is changed; it loses its strength and its amplitude. The mooing of the ox is different from the bellow of the bull. The capon does not crow.

The action of castration on the character and sexual instinct is also very definite. Castrated animals are more gentle, more docile, easier to train than the normal ones.

In other words, castration attenuates the sexual characteristics and allows the development of certain attributes of the other sex. The internal secretion of the genital glands favors the development of certain characteristics and inhibits others. These observations are applicable to human pathology.

The effects of castration can be decreased by grafts or injection of extracts of the interstitial gland. It is known that in frogs, the male presents a projecting thenar eminence which it rubs against the abdomen of the female during copulation and that ejaculation is brought about by the stimulation of these eminences. Extirpation of the testicles causes atrophy of these organs. When there is a secondary graft of testicle or the frog is injected with testicular extract, these projecting thenar eminences enlarge again. Ancel and Bouin have shown that the injection of interstitial extract in young castrated guinea pigs activates the growth of bone and prevents atrophy of the penis and seminal vesicles.

The action of the interstitial gland in the evolution of the young, as well as of the adult, of the sex is, therefore, very definite. This gland on one side assures the development of the genital organs, on the other, the appearance and upkeep of the sexual characteristics. We do not, however, know exactly how this mechanism is brought about.

I. SYNDROMES OF TESTICULAR INSUFFICIENCY.

Before studying the various clinical aspects, it is well to remember that testicular insufficiency causes different disturbances according to the age at which it occurs.

In very young individuals, in which the sexual glands are inactive, the organic changes which characterize the sex do not appear. In older subjects, in which the sexual organs are normally developed, the sexual characteristics persist, but become attenuated or regress.

Castration manifests itself by different symptoms according to its having occurred before or after puberty.

I. CASTRATION.

1.—BEFORE PUBERTY.—The results of castration before puberty are known by the study of Oriental eunuchs and a Russian religious sect, the Skotzis, voluntarily castrated. The operation is not, however, performed uniformally, so that the various observations are not always the same. In some only the testicles have been removed, in others, the penis and scrotum have also been excised and it is impossible to judge from the latter the condition of the external genitalia.

Castration before puberty shows a definite syndrome:

EUNUCHISM.—It is characterized by an abnormal growth. These individuals have a height above normal nearly reaching that of giants. It is, however, a mild gigantism oscillating between 1.80 and 1.90 metres and caused by an excessive development of the lower limbs, which is due to the late persistence of cartilage. It is often found, that even at an advanced age, these individuals still have non calcified epiphysis. When the height approaches the normal, there is a disproportion between the lower limbs and the rest of the body.

To these disturbances in the development of the skeleton are added hypoplasia or atrophy of the genital organs and the absence, more or less complete, of the secondary sexual characteristics. The penis is small and the prepuce very long, as in children; the scrotum does not develop; the prostate and the seminal vesicles are minute. The beard is scarce and the face is early covered with wrinkles, so that they appear as old men early in life. The hair, the eyebrows, the eyelashes are preserved, but become white very early, while in the axilla, chest and pubis the hairs are few or absent.[1] The poor development of the muscles give a rounded appearance. The flesh is soft, pale, flaccid. The neck is round, and smooth as that of a woman. The shoulders slant downwards and the thorax is narrow, in contrast to the width of the hips and pelvis. Hypertrophy of the breasts is frequent. The skin is soft and white. In other words, these individuals have a tendency to change towards the feminine type. The larynx stays narrow. Adam's apple does not protrude. The voice is high pitched. Finally, all sexual desire is absent. These individuals lack energy and cannot accomplish any strenuous work; they have no will power.

---

[1] It is believed that the hair of the head, the eyebrows and eyelashes are under the control of the thyroid, while the hairs of the beard, of the axilla and the pubis are under the dependence of the genital organs.

Castrated individuals have always been considered as indolent and mentally deficient.[2]

2.—After Puberty.—Observations of castration after puberty are rather unfrequent and the results are not well known. The development of the individual being ended there is no change in the skeleton. The height remains as it was before castration, for the epiphysis have already fused. The sexual attributes persist. The hairs of the beard gradually fall out, then grow again, but fewer and shorter; they persist, but are more scarce on the pubis and axilla. The feminine aspect is less pronounced. Adiposity is, however, very often present. The sexual instincts are not completely abolished. These individuals have erection and sexual intercourse. The ejaculations are made up of the secretions of the other genital glands.

They are calm, quiet. Psychic disturbances, if there are any, are to be blamed on the mental effect on these men of having lost the attribute of their sex (some castrated individuals have attempted to kill the surgeon who operated upon them) for all mental disturbances are absent in the Skotzis in which castration is voluntary.

II. UNDESCENDED TESTICLES.[3]

Two types of cases are met with:

1.—Those having the aspect, the attribute and the character of normal individuals. They have all evidence of being virile, except fecundity, and only the microscopic examination of the seminal fluid reveals the absence of spermatozoa.

---

[2] There is a somewhat similar clinical syndrome which has been described by Rummo in Italy under the name of gerodermia-genito-dystrophy which is characterized by an appearance of senility, genital atrophy, absence of development of the secondary sexual characteristics, an excessive height or an excessive development of the lower limbs. From a pathogenic point of view in spite of the predominance of genital disturbances, this condition cannot definitely be said to be due to a testicular insufficiency.

[3] Undescended or undeveloped testicle is often associated with lack of development of one of the lateral incisor teeth, usually on the opposite side.

Histological examination of the testicles of these types of cases shows an atrophy of the seminal tubules, but the interstitial gland is not affected. These cases have a simple spermatic insufficiency.

2.—Those having the appearance of castrated individuals.—Variot and Bezancon have shown that these individuals, in which the testicles are inside the abdomen, have all the characteristics of eunuchs. On histological examination of the testicles, the seminal tubules are found flattened and buried in connective tissue, while the interstitial gland is missing.

These cases have a double spermatic and interstitial insufficiency.

III. TESTICULAR INSUFFICIENCY DUE TO TOXIC OR INFECTIOUS LESIONS OF THE TESTICLES.

Testicular insufficiency is sometimes the result of a double orchitis with atrophy of the testicles. Certain cases of traumatic orchitis end in atrophy. Orchitis from mumps, Neisserian infection, lues, etc., show similar changes.

Certain infectious diseases (pneumonia, typhoid fever) possibly also tuberculosis (Poncet and Leriche) can affect the interstitial gland without causing an orchitis.

All these various diseases cause symptoms of testicular insufficiency which vary according to the age at which these lesions developed.

1.—If the patient has been affected before puberty he shows signs of infantilism. Evolution is arrested, the proportions of the body and its morphology stays infantile. The muscles are poorly developed and the cartilages persist.

2.—If the individual has been affected at puberty or immediately afterwards, the clinical picture is that of juvenilism. When he reaches the adult age, he keeps the attributes of an adolescent. The penis and the testicle keep the volume they had when the testicles became affected. The secondary sexual characteristics have not disappeared, but they have remained stationary. The pubic hairs which had begun to grow, cease to do so; the beard which was just beginning to grow never becomes more than a fine fuzz. The skin only indicates the age of the patient.

3.—When the individual has reached the adult age, the syndrome is different. Gandy has described it under the name of late or reversible infantilism. It is characterized by a regression of the genital organs accompanied by impotence, disappearance of erections, ejaculations and sexual desire. To these symptoms are added those of feminine characteristics: rounded form, abnormal development of the breast, widening of the pelvis.[4]

It seems to us logical to consider these three syndromes as the same condition occurring at a different age. There is still, however, much discussion on the limitations and origins of infantilism.

According to H. Meige, it is a syndrome characterized by an arrest in the development of the organism as a whole. That is by the persistence in an individual having reached or passed puberty of the morphological characteristics of childhood; small size, atrophy of the genital organs and absence of secondary sexual characteristics.

---

[4] These types of feminism correspond probably to the hermaphrodites of ancient statues. We must remember that true hermaphroidism is characterized by the coexistence in the same individual of an ovary and a testicle and is very exceptional. In order to determine this, careful histological examinations are necessary. The majority of hermaphrodites are pseudo hermaphrodites with hypospadia. The male pseudo hermaphrodites with feminism have a testicular insufficiency.

Souques considers that atrophy of the genital organs and the more or less complete absence of the secondary sexual characteristics are sufficient to define infantilism. Puberty separates man from the child and the other symptoms, the morphology of the body and the height are secondary and accessory. According to Souques the height is not controlled by the testicle, but by the pituitary. The experiments of Fichera have shown that after castration, there was a proliferation of the anterior lobe of the pituitary and that the skeleton grows in proportion.

This explains why certain writers, such as, H. Claude have refused to add the term infantilism to the syndrome of testicular insufficiency occurring in the adult and described by Gandy under the name of reversible infantilism, since these individuals have not the morphological characteristics of childhood. The dystrophy has not changed the morphology of the subject, having occurred after puberty, after the morphology had already completely changed. It has simply caused a regression of the genital apparatus and its adnexia, as well as its secondary sexual characteristics.

The origin of infantilism is also disputed.

Some, following Apert, consider it of thyroid origin. The testicle and the thyroid have a synergistic action. The thyroid atrophies in castrated young animals. The thyroid secretions enter in the development of the genitals, for in myxedematous subjects, the height does not change and the genital glands stay infantile. The thyroid has an opposite action on the skeleton to that of the testicle; in thyroid insufficiency, growth is arrested; in testicular insufficiency, it is exaggerated.

Souques believes that infantilism is always of testicular origin. The atrophy of the genital organs and the more or less complete absence of secondary sexual characteristics observed in thyroïd and pituitary infantilism, really are due to an insufficiency of the interstitial gland. In other words, the thyroid or the pituitary cause infantilism by the intermediary of the genital glands, either because the primary thyroid lesion or pituitary lesion acts by glandular synergy on the testicle, or that the arrest of development which results from it, affects the testicle, like all the other tissues and alters its internal secretion.

Sicard has an intermediary theory and believes that infantilism is due to both a thyroid and a testicular lesion. Lereboullet finally admits that late infantilism of adults can be the result of a primary pituitary alteration, whether the thyroid be affected secondarily or not.

II. SYNDROMES OF HYPERORCHIDIA.

The hyperfunction of the genital glands manifests itself by a great many changes which affect the organism as a whole.

In animals the testicles increase in size; the secondary sexual characteristics are modified; the feathers take on bright colors in birds; the horns appear on the deer at this period. The perineal glands secrete a strong and penetrating odor. The animals lose weight, are irritable, want to fight and are jealous.

In man, according to Carnot and Baufle, we can distinguish between permanent and paroxysmal hyperorchidia.

(*A*) Permanent Hyperorchidia.—This may be constitutional. Such individuals have certain peculiarities: the lips are thick and fleshy; the nostrils are open, the eyes bright. The neck is short; the back is broad, and these subjects are rather thin. The genitalia are very much developed: the testicles are swollen and resistant; the scrotum muscular and contracted. The hairs abundant all over the body.

Such men are quick, resist fatigue and like severe exercise. Their attitude and character is just the opposite of the castrated individuals.

Hyperorchidia can be produced by progressive training. It can be exaggerated by certain so-called aphrodisiac drugs (which cause a nervous stimulation, and it is hard to say whether it is the cause or the result of the glandular hyperfunction), or by a diet rich in nucleins and phosphorus. Finally, hyperorchidia may be morbid in certain tuberculous individuals, whose genital activity contrasts with the degeneration of the organism.

(*B*) PAROXYSMAL HYPERORCHIDIA consists in a genital stimulation which comes on in paroxysms and causes in man a sensation of general malaise, nervous irritability, a change in the psychic so that the only thing the individual thinks about is to satisfy his sexual desire.

These paroxysms are very often periodic, often seasonal (spring). In certain individuals it may be brought on by a memory, or lecture or a show. It is difficult in these cases to determine how much of this is due to the imagination and how much to the glandular hyperactivity. It seems, however, that the latter is the prime factor in certain subjects, who suddenly, without any stimulation, have a tremendous sexual desire and cannot return to work until this desire is satisfied. Hyperorchidia is often associated with other forms of glandular hypersecretion (hyperchlorhydria in particular).

INDICATIONS FOR TESTICULAR ORGANO THERAPY.

In spite of the experimental researches of Brown-Sequard, who had tried on himself with success the testicular extracts, this type of organo therapy has not proved satisfactory and has practically been abandoned to-day.

Its efficacy in testicular insufficiency is doubtful. In adults, it has been used against impotence, where it probably only has a psychic action. In children, it is said to have helped growing pains.

The extract of the dried gland is given in doses of from 1 to 4 grams daily.

CHAPTER XI.

PATHOLOGY OF THE OVARIES.

FUNCTIONS OF THE OVARIES.

The conception of an internal secretion of the ovary believed by Brown-Sequard to be the only way to explain the results of ovarian castration, has been definitely established in France by de Prenant and his students and Simon, Ancel and Bouin.

The external secretion of the ovary is represented by ovulation. Its internal secretion is due to two types of glands: the corpus luteum and the interstitial gland.

(*a*) The corpus luteum is a special tissue, which fills the cavity left by the ovule. It is due directly to the transformation of the follicular epithelium. That it is a glandular structure is not questionable; it is made up of large cells filled with fats, pigments and cytoplasmic formations, characteristic of cellular elements.

(*b*) The interstitial gland or more correctly the interstitial cells develop from the false yellow bodies. These false yellow bodies develop from the atresic follicules from which the ovule has not been liberated and which has been resorbed and is changed into strands of cells which Regaud, Bouin and Limon have shown to be of a glandular nature. These are filled with fats, but do not contain any lutein. They are homologous to the interstitial glands of the testicle.

The interstitial gland secretion is, therefore, obtained from the resorption of non liberated ovules.

The development of this gland varies in different species of animals; in the woman it is rudimentary.

* * * * *

The internal secretion of the ovary controls menstruation, fecundation and gestation. Under normal conditions, the secretions of the corpus luteum causes the liberation of the ovule. According to Fraenkel, it has a vaso dilatation action on the blood vessels of the uterus and prepares it to receive the fecundated ovum and assures the ulterior development of the embryo. The experimental destruction of the corpus luteum causes an atrophy of the uterus and tubes. In case of gestation, sometimes abortion, sometimes absorption of the egg occurs. By inoculating rabbits with the extract of corpus luteum a serum has been obtained which prevents gestation.[1]

The internal secretion of the ovary also has a sexual function. X-ray of the ovaries of female rabbits as performed by Bouin, Ancel and Villemin causes an atrophy of the ovarian follicles and prevents the formation of corpus luteum. It acts then just as castration and prevents the development of the genitalia and the mammary glands.

The injection of corpus luteum in castrated females causes a congestion of the genital organs resembling the phenomena of rut. (Marshall and Jolly).

The nature of the products elaborated by the internal secretions of the ovary are unknown. All that we know is that the extracts of ovary have certain definite physiological properties. They have a cardio vascular action, decrease the blood pressure, increase the number of red cells and the percentage of hemoglobin. They have also an action on the respiratory and digestive functions. They increase the renal secretions. They act as stimulants of nutrition and increase the elimination of calcium, phosphates and nitrogenous products. Hallion has shown that ovarian extract causes a vaso dilatation and an increase in the volume of the thyroid, the proof of a synergy of the thyroid and ovary which we find clinically.

---

[1] It is a fact well known to veterinarians that the persistence of a corpus luteum of pregnancy is a cause of sterility in cows. Removal of the cyst restores fertility. The same fact has been noted in women. It is possible that the persistence of a corpus luteum of pregnancy has something to do with the so-called "missed abortion."

Finally, the ovarian extracts are very toxic, much more so than the extracts of other glands. This toxicity is due to the corpus luteum (Lambert). Some physiologists believe that the ovary has an antitoxic action, the gland fixing and transforming the toxins brought to it by the blood stream.

Loisel does not believe that we can dissociate these various ovarian functions. The toxins elaborated by the ovary are changed into products, some of which are eliminated with each ovule and help in the sexual reproduction, and the others are re-absorbed by the organisms as internal secretions and act on menstruation, fecundation or gestation, some on the organism as a whole and cause the appearance of the sexual characteristics and rut.

I. SYNDROMES OF OVARIAN INSUFFICIENCY.

They may follow:

1. Ovariotomy.
2. Normal menopause.
3. Congenital or acquired ovarian insufficiency.

I. POST OPERATIVE OVARIAN INSUFFICIENCY.

The changes in the organism, following the removal of the ovaries, vary with the age of the patient.

(*A*) Precocious removal[2]. The observations of these cases are very few. Following the removal of the ovaries, the external genitalia and the uterus atrophy. Menstruation does not appear. There is an absence of development of the secondary sexual characteristics: the breasts remain infantile, the axillary and the pubic hairs are few or absent. The morphology deviates from the feminine type: the pelvis remains narrow, the pubis and the buttocks lack fat. The limbs elongate. Certain Hindoo women, about 25 years old, castrated in childhood, were observed by a doctor Roger to have no feminine characteristics. They were big, strong, muscular, without any breasts or pubic hairs.

---

[2] Early castration before puberty is well known to veterinarians who perform it on certain animals (sows and cows). The removal of the ovaries causes an atrophy of the uterus; it prevents the appearance of rut. Castrated animals grow fat very rapidly.

(*B*) Castration after puberty.[3] The effects of castration after puberty in women has been studied in France by LeBec, then by Richelot, Jayle and Tuffier, etc.

While simple hysterectomy, without removal of the ovaries, often only causes very minor symptoms; double castration causes a series of accidents commonly known under the name of post operative or artificial menopause.

These disturbances occur either a few months after operation, or several years afterwards, varying according to the age of the patient, her character and her previous nervous state. The more important are the following:

1. Atrophy of the Uterus, More Rarely of the External Genital Organs.—The menses are not always suppressed. Some women after a double ovariotomy have continued to menstruate. Out of 45 women studied from this point of view by Jayle, only 28 had ceased to menstruate. Some, for a certain length of time, still have periodic flow. Others have vicarious menstruation. In others, the menses are missing, but are replaced by heat waves, malaise, migraine, and a slight rise in temperature.

---

[3] In adult animals, castration often causes an atrophy of the genital system and decreases the sexual appetite. In the cow it will greatly increase the quantity of milk and prolong the lactation period. When lactation ceases the animal puts on weight and the genitalia atrophy.

All these facts show that the internal secretion of the ovary has not an exclusive action on menstruation.

2. Attenuation of the Secondary Sexual Characteristics—The breasts atrophy, hairs appear in abnormal places. The voice becomes manly. The sexual appetite varies: it may be decreased, but it can persist and even become exaggerated in certain women.

3. Tendency to Obesity.—Castration is often followed by a rapidly progressive adiposity, in spite of dietary restrictions. It starts from the abdomen and spreads to the neck, thorax and limbs.

'4. Vaso Motor and Nervous Disturbances.—They are quite frequent and are those which worry the patient most. The waves of heat are the most annoying. They come on suddenly, without any particular reason either in the day or at night. Suddenly the patient feels terribly warm in the face, the ears buzz, and the face becomes congested. After four or five minutes the attack ceases: the face becomes pale and the body is covered with sweats. These attacks occur several times a day. They are most pronounced at the time when the menses should appear and may persist for several years after operation.

They also often complain of pain: some have lumbar pains, radiating in the legs; others have pelvic neuralgias. Headaches and migraine are frequent, often persistent, coming on in paroxysms. Some women complain of palpitations, with pain and vertigo. These symptoms are usually associated with a slight increase in blood pressure, for arterio sclerosis often develops in women after castration.

Nervous disturbances may be varied: insomnia or restless sleep, with nightmares, changes in the character: irritability, tendency to sadness, neurasthenia, melancholia. Physical and mental asthenia may sometimes be very pronounced. According to Jayle the loss of memory is very common. Finally, following castration a real psychosis may develop: hysterical attacks, erotism at the time of the menses, acute mania, hallucinations, etc.

These symptoms of artificial menopause last a variable period of time. It is not uncommon to see them disappear with or without treatment, but they may last, attenuated, for several years. In some young women, they may disappear and then return at the time when the menopause would normally have occurred.[4]

All these changes following castration are not constant and are not found in all cases. Certain surgeons, Segand, Quenu, J. L. Faure, Delbte, do not believe in post operative menopause phenomena and consider them to be insignificant and of no more importance than the natural menopause. When they are found, they consist mainly of waves of heat, slight nervous excitability and compatible to a normal existence and susceptible of disappearing in time. The severe cases are very rare and are only found in very nervous women or in cases of hyperthyroidism. They are exceptional in hypothyroidism, in which cases the menses are late and the sexual phenomena are attenuated. Sometimes these changes are more marked in women nearing the menopause than in young women.

For this reason the pathogenesis is very much in doubt. Some writers refuse to believe that they are due to ovarian insufficiency and are really indications of hyperthyroidism. The suppression of the ovarian secretion, by disturbing the glandular equilibrium, causes a complex syndrome in which can be recognized, not only signs of thyroid hyperfunction, but also adrenal hyperfunction. The sclerosis, the high blood pressure, the angina, certain atheromata appearing at the menopause, are probably due to a hypersecretion of the adrenals secondary to an ovarian hypofunction.[5]

---

[4] In general it can be stated that the younger the patient or the more stable the nervous equilibrium, the less severe will be the manifestations of the artificial climacteric.

II. DISTURBANCES OF THE NORMAL MENOPAUSE.

CRITICAL AGE SYNDROME.

They are the same symptoms but attenuated, of post operative menopause. Some women have their menses late, then suppressed without the slightest disturbance. Some only have a tendency, after the disappearance of the menses, to become obese. The fat invades the whole body or may localize in the neighborhood of the genitalia: hips, buttocks, upper part of thigh and abdomen, while the arms and legs keep their shape.

Not so commonly, the sexual characteristics of the woman disappear; they become virile; the features become masculine; hairs appear on the upper lip and chin; the voice becomes deeper; the disposition changes.[6]

In other women, a series of disturbances occur:

Migraine appears in place of the menses accompanied by palpitations, waves of heat, insomnia, difficult digestion.

Vertigo and pains; pseudo angina, or true angina for the menopause may be accompanied by atheromata or arterio sclerosis.

---

[5] A number of experiments have proven that the various stages of the genital life of the woman are under the control of several glands of internal secretion. According to Gautier the menstrual blood differs from the normal in that it contains a large quantity of arsenic. Normally this substance accumulates in the thyroid and takes some part in the development of hair and of menstruation. At puberty arsenic in man localizes in the sebacious glands and causes the development of the beard and hairs, so that this in man is the equivalent to menstruation. During pregnancy, due to the suppression of the menses the arsenic accumulates in the thyroid which increases in size and in the skin which becomes abnormally pigmented.

[6] These phenomena resemble those observed in animals. The feathers of certain old females become more brilliant and look more like those of the male. Old hens which do not lay any eggs have spurs on their legs similar to those of the roosters.

Attacks of paroxysmal tachycardia which are very painful.

Abnormal pigmentations of the lids, face and so-called ovarian spots.

Delpech, then Dalche, have also considered as symptoms of the menopause:

Tetany.

Acroparesthesia.

Dercum's disease.

Chronic rheumatism.

Skin infections; eczema, purigo, etc.

III. CONGENITAL OVARIAN INSUFFICIENCY.

This results in ovarian infantilism comparable to testicular infantilism. It is found in small women whose height rarely exceeds 1.50 meters and weight 40 or 50 kilograms. They have a malformation or an arrest in development of the genital organs; the uterus is infantile. The secondary sexual characteristics are missing; hairs are missing in the axilla and pubis, or are very scarce. The breasts do not develop. Amenorrhea is the rule and co-exists with a slight degree of obesity.

IV. OVARIAN INSUFFICIENCY AT PUBERTY.

Rokitansky considers chlorosis as an indication of ovarian hypoplasia, and Spillman, Etienne and Demange also believe that it is due to a hypo function of the ovary. Whatever the exact nature of this pathological condition, it is certain that genital disturbances are constant in chlorosis and that the condition of the blood is improved by marriage, due to the development of the genital functions, and that the re-appearance of regular menstruation coincides in general with the clinical cure of the patient.

V. ACQUIRED OVARIAN INSUFFICIENCY.

Insufficiency of the ovary resulting from an alteration of the ovaries following a genito urinary disease or a general disease can manifest itself in several ways.

1. Dysmenorrhœa.—Ovarian dysmenorrhœa, independent of any appreciable lesion of the uterus or genital organs, manifests itself by painful and difficult menstruation. There are severe abdominal pains, associated with waves of heat, painful sensations in the breasts and general malaise occurring anywhere from 3 to 7 days before menstruation. A few hours before the flow begins, the pains become more severe and radiate towards the anus and rectum taking on very often the character of a pelvic neuralgia. Many of these women are sterile or only become pregnant very late.[7]

2. Nervous Disturbances.—(*a*) Each menstrual period causes severe headaches or migraine, accompanied by vomiting, and renal or hepatic congestion and various myalgias and neuralgias. These symptoms become much less severe as soon as the periods are over and re-appear just before the next.

In some women, there is a frontal or periocular headache, very painful and very persistent and which continues between the periods and becomes more intense at the time of the flow. At this time, the patients have a thumping sensation in their head, vertigo, visual disturbances, which oblige them to stay in bed. Dalche suggests that this headache may be due to a functional disturbance of the pituitary due to a disequilibrium of the ovary.[8]

---

[7] As a rule when dysmenorrhœa is not due to inflammation or mechanical obstruction, it is a manifestation of hyper pituitary stimulation. The secretion acting during menstruation as it does in labor causes exaggerated uterine contractions which are painful.

[8] I believe this observation to be correct. Medication designed to overcome excessive pituitary action during menstruation will often relieve the headaches.

(*b*) To the nervous disturbances occurring in the ovarian insufficiency are associated certain genital psychoses, observed very commonly, however, at puberty, or at the time of the menses. The psychoses of puberty manifest themselves in most cases by mental confusion; less commonly by acute mania or melancholia.

The mental psychoses appear a few days before the menses and only disappear after they are over. The usual type is erotism or mysticism.[9]

The ovarian origin of these cerebral disturbances is proved by the fact that they coincide with other symptoms of ovarian insufficiency and that they are improved by ovarian organo therapy.

3.—OBESITY.—This may be observed at various stages of the genital life of women and sometimes may be due to ovarian insufficiency (Carnot).

Post nuptial obesity, which comes on a few months following marriage, is probably due to the glandular changes brought about by sexual activity.

Gravid obesity is very frequent. Many women grow fat at the beginning of pregnancy. The adiposity can persist after delivery in women who previously were thin.

VI. THYROID-OVARIAN INSUFFICIENCY.

Any disturbance of the thyroid functions in infancy or adolescence may affect the genital system. The hypofunction of the ovary is then secondary to a hypothyroidism. In these patients are found associated symptoms of both thyroid and ovarian insufficiency.

They are small women, showing a delayed physical development, pilary disturbances and lowering of the body temperature. They are apathetic, subject to headaches, etc., and puberty is delayed. The uterus stays infantile.

---

[9] Here again the pituitary must not be considered blameless.

The menses are irregular and scanty. Sometimes, at the menstrual period, they have symptoms of hyperthyroidism: tachycardia, tremors, nervosity, etc., indicating a certain degree of thyroid instability. The menopause in these women occurs very early in life. They cease menstruating at 25 or 30.

In other cases, there is a hyperfunction of both the thyroid and the ovary. The menses are early, last a long time and are very abundant. In some cases, there is alternatively hypo and hyperactivity of the ovaries: the menses are ahead of time, but are scarce or late and excessive. There is a disequilibrium of the ovarian functions or ovarian ataxia, as described by Jayle.

TREATMENT OF OVARIAN INSUFFICIENCY.

1.—Ovarian graft would appear to be the most satisfactory therapeutic method to prevent the various phenomena following the removal of the ovaries.

Grafts were first attempted on animals by Knauer and Rubinstein, and in France by Limon, who showed that the graft went through two distinct stages; first of degeneration, then regeneration. Then Sauve found that the graft, while histologically appearing to functionate, has a different structure from the normal ovary and resembled ectopic ovaries. All the physiologists agree that homogenous and heterogeneous graft nearly always fail and that auto graft is the only method which has any chance to succeed.

Human grafts were first attempted by Morris. In France Mauclaire, Delageniere, Tuffier and Sauve have attempted it in the tubes or in the broad ligament, or in the subcutaneous cellular tissue and even in the peritoneum (Tuffier).

In a few cases the graft has been followed by an improvement of the symptoms and a re-establishment of the menstrual flow. Pankow has shown histologically the vitality of a graft after three years.

In very exceptional cases the graft has been followed by pregnancy. The observation of Morris is classical: a woman on whom he had performed a double ovariotomy and at the same time a heterogeneous graft in the broad ligament, became pregnant four years afterwards and gave birth to a full time child.

These observations are, however, not as convincing as we might think, for the return of menstruation after castration, not followed by graft, is not exceptional and, furthermore, small ovarian remains, or supernumerary ovaries, left during the castration can explain the ulterior pregnancy.

As a matter of fact, most grafts are failures. Some are painful and periodically become congested and painful (Tuffier) so that while this method is of interest from a biological and theoretical point of view, nearly all surgeons have given it up.

2.—Ovarian organo therapy can be used:

(*a*) By using the fresh gland of the sheep in doses of from 2 to 3 grams daily. This method of administration is usually not well tolerated.

(*b*) Ovarian powder in doses of from 0.10 to 0.50 centigrams daily, or the extract of the corpus luteum in smaller doses (0.02 centigrams for 5 or 6 days). These are the most commonly used preparations.

(*c*) Glycerin extracts for injections do not appear to be any better.

Ovarian organo therapy only succeeds in cases of hypofunction of the ovary. It can then attenuate the menstrual pains, regulate the menses, decrease the obesity, even improve the psychoses of puberty or menstruation.

In artificial or natural menopause it cannot take the place of the missing internal secretion, so that the results are variable. Sometimes there is a temporary improvement which only lasts as long as the medication is kept up; sometimes it is without effect. Furthermore, the vaso motor or nervous phenomena coming on after removal of the ovaries or at the menopause are really indications of thyroid re-actions to ovarian insufficiency and are best treated as such. Hematoethyroidin or even extracts of thyroid in very small doses, regulate the function of the thyroid.

In thyroid-ovarian insufficiency, ovarian extract alone is often efficacious. Sometimes mixed ovarian and thyroid medication or thyroid alone causes a marked improvement in these cases.

II. SYNDROMES OF OVARIAN HYPERFUNCTION.

Women with hyperfunction of the ovaries have, according to Dalche, certain characteristics. They are well shaped, without excessive weight; they are pale; their eyes are bright; the features very expressive and mobile. They have a marked appearance of sexuality.

This is sometimes appreciable in girls in which puberty occurs early and is accompanied by hysterical attacks sometimes re-occurring at each menstrual period.

This condition is often hereditary. These women are found to have begun to menstruate early, had many children and a late menopause. The usual symptoms of menstruation are exaggerated. The menses are abundant from the first day on and last 8 or 10 days. There is considerable pelvic congestion, which manifests itself by a sensation of abdominal weight, cramps, desire to urinate, hemorrhoids, painful breasts. The disposition is very irritable and varies from one minute to the other. The sexual sensations are exaggerated during the menstrual period.

To this hyperfunction of the ovaries are connected certain metrorrhagias appearing at puberty or at the menopause.

I. METRORRHAGIA OF PUBERTY.

These are characterized by more or less abundant hemorrhages at the time of the menses (menorrhagia) or in the interval (metrorrhagia) accompanied by pains in the pelvis radiating in the lumbar region of the thighs. The pains precede the hemorrhages, or may occur in the interval. In spite of the loss of blood the general health stays good, but at a certain time occurs signs of anemia, so that these patients are mistaken for chlorotics.

These metrorrhagias may disappear when menstruation is definitely established; very often they keep on having abundant menses.[10]

In some cases the hemorrhages persist and are comparable to those observed in fibroids necessitating operative intervention.

II. METRORRHAGIA OF THE MENOPAUSE.

It is found in women between 40 and 50 having had, or not, several pregnancies, or in unmarried sterile women without any genital history.

During the first stage, which may last several months and even several years, menstruation is irregular; the menses are abundant one month, the next they are absent. Then occur menorrhagias, lasting longer and longer and which resist the usual treatment: hot irrigations, tampons, curettage, etc. They are sometimes accompanied by neuralgias and end up by severe anemia.

---

[10] These early menorrhagias and metrorrhagias are explained by the lack of harmony in the retrogression of thymus activity and the evolution of the ovarian stimulation.

The cause of these hemorrhages escapes detection. They are not caused by a general disease, nor by a cardio vascular affection, nor by a blood abnormality. There are no lesions of the genital organs. For this reason they are called essential menorrhagia.

Their etiology has been very doubtful. Some believe that they were due to a metritis, but Richelot has shown that they were independent of all infections; others believe that a sclerosis of the uterus is the cause, but this has never been verified by histological examination (Pankow). Finally, they have been blamed on adenomatous transformation of the uterine mucosa, but we know to-day that this transformation is a physiological modification occurring in the interval between the menses.

At present it is believed that these hemorrhages are due to a disturbance of the internal secretion of the ovary. The conception is based on certain facts:

1.—These hemorrhages are observed at the two extremes of the genital life, when menstruation begins or ends. That is when the ovarian secretion is defectively regulated.

2.—They are abolished by the removal of the ovaries (Lawson-Tait-Bouilly). Castration cures the majority of the cases.

3.—Forgue and Massabuau have found in these patients histological lesions of the ovary, which consisted in a marked increase in the number of atresic follicles, very scarce normally. Each atresic follicle is made up of a neo formation of lutein cells, so that this condition is really a hypertrophy of a gland of internal secretion.

This gives rise to a quantity of abnormal hormones, which causes the hemorrhages and modifies menstruation.

It is still hard to say why this only occurs at puberty or at the menopause.

TREATMENT.

Hyperfunction of the ovary can be treated:

(*a*) Hygiene.—This consists in preventing the pelvic congestion, by a careful diet, eliminating all stimulating foods or drinks and avoiding constipation.

(*b*) Medications.—The usual hemostatics, ergot, calcium chloride, hamamelis, hydrastis are usually unsuccessful. Very hot vaginal irrigations or ice on the hypogastrium may be beneficial.

The injection of blood serums (pure serum, antitoxin, etc.) subcutaneously in doses of 20 to 30 centigrams are often efficacious. Unfortunately, their action is only temporary.

(*c*) Organo Therapy.—Ovarian extract is contra-indicated. Thyroid, pituitary and mammary organo therapy have a definite anti hemorrhagic effect. Clinical observation has shown that thyroid extract in small doses 0.005 to 0.01 centigrams daily) seem to regulate the thyroid functions and cause a cessation of the genital hemorrhages.

Dalche advises the use of pituitary extract which has an inhibitive action on the ovary and which, furthermore, increases the coagubility of the blood and causes a contraction of the uterus and its blood vessels.

Mammary extract is very advisable by reason of its functional antagonism between the breast and the ovary (Bell, Crouze, Batuaud, Pochon).

During the hemorrhages, it can be administered in doses of 0.50 centigrams 3 or 4 times a day. Between the hemorrhages the doses can be reduced to twice daily. Just the opposite of the ovary, mammary extract has a decongestive action on the uterus.[11]

(*d*) SURGICAL.—If the hemorrhages persist or become dangerous because of the resulting anemia, the only thing to do is castration of the ovaries, or the removal of the uterus and ovaries, or sterilization by means of radiotherapy.

---

[11] Here is the indication par excellence for thymus therapy to oppose the ovarian activity. (Dose: 0.50 centigrams twice daily).

CHAPTER XII.

PATHOLOGY OF THE MAMMARY GLAND.

Is the breast a gland of internal secretion? We cannot yet say for sure: the internal secretion of the mammary gland has not yet been proved, by histological or physiological facts.

A certain number of clinical observations seem to prove that there is a synergy between the mammary gland and the thyroid on one side, and with the genital glands on the other.

One fact has for a long time attracted attention and that is the atrophy of the breasts in Basedow's disease. It is true that this atrophy coincides with that of the genital glands. Inversely, however, hypertrophy of the mammary gland has been observed in myxedema (Apert, Sainton and Fernet). This relationship between the thyroid and the mammary gland has not yet been explained.

Another curious fact is that reported by Djemil-Pacha of a man, having a bilateral mammary hypertrophy and in which the removal of the breasts was followed by all the symptoms of post operative myxedema.

* * * * *

The relationship between the breasts and the genital organs is better known. An increase in the size of the breasts is noticed at three periods, in which the breasts are physiologically active; at birth, at puberty and during pregnancy. In the new born during the first few days of existence the mammary gland secretes: this, according to Ancel and Bouin, is due to a hormone in the mother's milk originating from the placenta.

At puberty the increase in the size of the breasts appears at the same time as the other secondary sexual characteristics. This growth is controlled by the corpus luteum.

In the same way, the congestion of the breasts preceding menstruation, are due to the corpus luteum. The prickling sensations and the tension of the breasts disappears after menstruation; that is, at the time when the corpus luteum degenerates.

The increase in the size of the breasts during the first few months of pregnancy is also due to a hormone coming from the corpus luteum, which lasts much longer than that of a corpus luteum of menstruation. This is a physiological hypertrophy, which regresses after delivery.

Such are the physiological reactions of the mammary gland to the action of the genital system.

Next to these physiological facts, are certain pathological observations, the mechanism of which is still unknown and which we will successively study in woman and in man.

I. MAMMARY HYPERTROPHY AT PUBERTY IN WOMEN.

This is a peculiar affection found in girls between 11 and 16.

The breasts increase in size; they become firm and prominent. Their consistency is uniformly hard and resembles that of the normal breast. The skin is freely movable.

Very quickly the breasts, whose volume increases, become pendulous. The skin becomes distended and the veins dilate. The nipple flattens out or becomes invaginated. In a few months these breasts become two enormous sacs, which fall as far down as the umbillicus and even in some cases to the level of the knees. This mammary hypertrophy has no ganglionic reaction. There is no secretion from the breast. There is at first a sensation of discomfort, then fatigue. The patients are smothered and have considerable difficulty in breathing.

This condition is not only a deformity but cripples the patient. It brings on severe general symptoms that the volume of the breast alone could not explain. These patients emaciate, become pale, have gastro intestinal disturbances, often diarrhea and die, either from some intercurrent affection or from a local complication: abscess, gangrene, fibroma, or cysts. In these girls the menses do not appear or are irregular and painful. If menstruation has already set in it disappears. Pregnancy is the exception and rarely goes to term.

In a few cases the condition is unilateral:

The histological examination of the gland, does not reveal any tumor or abnormal formation. Its structure is that of a normal gland in which the lobes and the periglandular tissue is abundant without any histological changes. According to Caubert, it is a "gigantism of the breast."

The pathogenesis is still obscure. We know that the condition is often hereditary.

Because this condition appears at the time of puberty Pasquier believes that it is due to a disturbance of the ovary and perhaps to an excess of internal secretion. The resorption of the ovules, particularly pronounced at puberty, results in decrease in the external secretion of the ovary; that is, ovulation at the expense of the internal secretion and this is equivalent to a resorption of toxic substances, which results in severe disturbances. The lack of external secretion explains the disturbances in menstruation and the sterility (Delbet). A few autopsies have revealed enlarged or diseased ovaries.

The regression of the mammary hypertrophy is rare and generally incomplete. It is progressive and the severity of the general symptoms necessitates intervention. Ovarian organo therapy being without effect, the only thing to be done is amputation of both breasts which causes, strange to say, a return of the health.

II. MAMMARY HYPERTROPHY IN MAN.

(*a*) It occasionally happens that at puberty in young boys there is a hypertrophy of the breasts which after a time regresses. It looks as if the testicle secreted a cytogenic hormone of the breast, the action of which is inhibited by the ultimate testicular secretion.

(*b*) The development of the breasts is frequent in the various syndromes of testicular insufficiency observed after castration or following orchitis with testicular atrophy. It is found in individuals with a poor musculature and in which the genital glands are atrophied and with a large pelvis. It, therefore, is one of the elements of feminism.

(*c*) Sometimes cases of unilateral hypertrophy are observed in man following a trauma to the scrotum (traumatic orchitis, atrophy of the testicle after a wound of the cord, contusion of the scrotum with hematoma), usually on the same side. It is very hard to explain this; as a rule the traumatism is very slight and does not cause any atrophy of the gland and that, furthermore, unilateral castration or a diffuse glandular destruction does not cause gynecomastia.

(*d*) Hyperplasia of the mammary gland is also sometimes met with without any trauma, or any inflammation of the testicle or any stigma of degeneration of the genitalia, or testicular insufficiency, in young soldiers. It may be unilateral or bilateral. It is found according to Puech once in 13,000 cases. The breast presents the appearance of those of an adult woman with an areola and a well-formed nipple.

There is nothing so far to prove that this is due to a disturbance of the internal secretion of the testis or any other gland.

CHAPTER XIII.

PLURIGLANDULAR SYNDROMES.

The glands of internal secretion make up a system, each one of them being more or less dependent on the other.

They are connected with each other by synergy, antagonism or supplement each other, so that the lesion of one gland causes modifications in others.

There are definite proofs of this glandular relationship:

1.—EXPERIMENTAL.—We know that there is a hypertrophy of the pituitary after castration and an atrophy of the testicle after the removal of the thyroid. The thyroid increases in size after the removal of the ovary.

2.—PHYSIOLOGICAL.—The injection of corpus luteum causes a marked vaso dilatation of the thyroid, and that of the pituitary a vaso constriction (Hallion).

3.—ANATOMICAL.—Autopsies on myxedematous patients, or patients with Basedow's disease show lesions of several glands: atrophy of the genitalia, hypertrophy of the pituitary, frequent hyperplasia of the thymus, an increase in volume of the pituitary is the rule in Addison's disease, as is testicular or ovarian atrophy in acromegalia. In the syndromes attributed to one gland, autopsy always shows pluriglandular changes.

Myxedema, Basedow's disease, Acromegalia, do not, however, belong to the group of pluriglandular syndrome.

* * * * *

The term pluriglandular syndrome suggested by Claude and Gougerot in 1907 must be understood in the clinical sense. These writers have insisted that only the clinical examination of the patient, by detecting various morbid disturbances, indicating alterations of several glands allows us to make the diagnosis of pluriglandular syndrome. The pluriglandular syndromes, says Sourdel, are "characterized by the co-existence, at the time the patient is examined, of different symptoms which are believed to be due to a disturbance in the function of the system of the endocrines." The pluriglandular syndromes constitute not only an anatomical conception but a clinical conception.

CLASSIFICATION OF PLURIGLANDULAR SYNDROMES.

The pluriglandular syndromes are more or less complex according to the number of glands affected: the order of succession and the degree of the lesions. They manifest themselves, theoretically at least, by signs of insufficiency, or hyperfunction of several glands in various proportions.

We know the physiology and the relationship of the endocrine glands, but they are still too indefinite to allow us to establish a pathogenetic classification of these various and multiple pluriglandular associations. An anatomical classification would also be unsatisfactory, for our histological methods do not allow us to appreciate sufficiently the functional conditions of the glands, and pathological anatomy does not always confirm the glandular lesions suspected during life.

For this reason the clinical classification is the only one which has been attempted up to now and from this point of view we can divide the pluriglandular syndromes into three groups.

FIRST GROUP.

It is characterized by a primary alteration of one gland and a secondary action on several others. In the symptomatology there is always the predominance of the disturbance of one gland. The majority of these syndromes have been previously mentioned. We will simply recall a few:

1.—PLURIGLANDULAR SYNDROMES WITH THYROID PREDOMINANCE.—Basedow's disease with ovarian insufficiency and amenorrhea.

Myxedema with testicular atrophy.

Myxedema with mammary hypertrophy.

2.—PLURIGLANDULAR SYNDROMES WITH PITUITARY PREDOMINANCE.—Gigantism with infantilism. Acromegalia associated with glandular insufficiency (amenorrhea) or with symptoms of hyperfunction of the adrenals: arterial hypertension, and Atheroma (Claude) or hyperplasia of the thyroid and adrenals. (G. Ballet and L. Lavastine).

3.—PLURIGLANDULAR SYNDROMES WITH OVARIAN PREDOMINANCE.—The most important are the thyroid ovarian syndromes:

Hypertrophy of the thyroid at puberty or during pregnancy.

Thyroid reaction associated with ovarian insufficiency. These symptoms resemble Basedow's disease. In some cases it may give all the symptoms of a true Basedow's disease.

SECOND GROUP.

This is characterized by the association of two uniglandular syndromes, each of which having its peculiar characteristics.

This is the case:

Exophthalmic goitre, associated with Addison's disease.

Exophthalmic goitre, associated with acromegalia (Murray) or with gigantism (G. Ballet).

Myxedema, following Basedow's disease.

Myxedema, associated with acromegalia (Burchard).

THIRD GROUP.

This is characterized by the association of several uniglandular syndromes without any marked predominance of any.

This group has been studied by Claude and Gougerot in the case of a man first affected by genital atrophy and loss of hair on the pubis and axilla and who in a few years showed a progressive asthenia accompanied by arterial hypotension, with thickening of the skin and an abnormal pigmentation of the skin. Autopsy revealed lesions of several glands: thyroid, testicles, adrenals, pituitary; thus explaining the pluriglandular symptomatology of the patient. In this observation, there was no predominance of any one gland.

ETIOLOGY.

Pluriglandular syndromes may be the result, more or less delayed, of an infection: typhoid, rheumatism, scarlet fever, malaria, of alcoholism, of renal or hepatic lesions (cirrhosis, biliary, hypertrophy, etc.) of acquired or congenital lues and of tuberculosis.

A certain predisposition of the endocrine system seems to be necessary. They are more often met with in men with a moderate sexual appetite or women with irregular genital functions.

SYMPTOMATOLOGY.

One of the most frequent types is the syndrome of pluriglandular insufficiency of the thyroid, testicle and adrenal.

The condition starts very gradually in individuals, who up to then had had a normal activity and good health. They become listless, complain of general weakness or have genital disturbances: sexual desire decreases and finally disappears. At the same time the skin takes on a yellowish color and becomes slightly infiltrated.

Once the syndrome established the patients take on a characteristic appearance. They appear like old men. The beard has fallen out and only a few hairs, or none at all, are left. The hairs do not fall out, but become dry, break easily and turn white prematurely. The eyelashes and eyebrows sometimes fall out. The skin is wrinkled and at the same time thickened and dry, often pigmented; it appears dirty when the pigmentation is slight and diffuse.

The body shows a certain degree of adiposity; the skin is fine, white and slightly greasy to the touch. The regions normally pigmented are frequently discolored. It is not rare to find on the body spots of pruritus, surrounded by an area of pigmentation. Often the morphology approaches the feminine: hypertrophy of the breasts, widening of the hips, infiltration of the pubis with fat. The hairs are missing or rarified in the axilla, on pubis and on the limbs.

The genital organs are atrophied; the penis is decreased in size; the testicle the size of a pigeon's egg and soft. Sexual desire nearly always disappears.

From a functional point of view the patients complain of a marked asthenia: muscular strength is very much decreased. They are apathetic or indifferent. Their character is irascible. Some cry without any particular reason; some realize their degeneration and become neurasthenic. They are extremely susceptible to the cold and even in the summer time still feel frozen. With this is associated a decrease in the blood pressure.

In women the symptoms are comparable. The feminine shape is lost. The breasts become atrophic; the pelvis becomes narrower. The hairs in the pubis and axilla fall out, while the chin is covered with a fine fuzz.

Menstrual disturbances are nearly always present; the genital organs regress; the uterus becomes of the infantile type. In other words, in both sexes there is a loss of the secondary sexual characteristics and the evolution towards a neutral type.

This is the most frequent type, but there may be variations:

(*a*) The affection may begin with changes in the pigmentation accompanied by vertigo and lassitude. This pigmentation is more pronounced than in the preceding type, and resembles that of Addison's disease. It differs, however, in its location, for it usually affects the non pigmented parts.

(*b*) In other cases, particularly in women, the symptoms of hypothyroidism predominate. Following the cessation of the menses appear signs of myxedema: adiposity, thickening of the skin, yellowish and puffed faces. As in the preceding cases there are disturbances of the growth of the hairs; hypotension and asthenia.

EVOLUTION.

This condition evolutes very slowly and lasts for a long time. There are periods of improvement in summer or following organo therapy. They usually die of cachexia, showing a progressive asthenia, comparable to Addison's disease or following some intercurrent infection, very often tuberculosis.

DIAGNOSIS.

The interpretation of this thyroid-testicular-adrenal syndrome has been very much disputed. According to which one of the three glands was most affected, writers have described it under different names.

It has, for instance, been called: abortive myxedema, pseudo myxedema, reversible infantilism, feminism with testicular atrophy, etc.

As brought out by H. Claude, these names give an incorrect pathogenic interpretation.

The term infantilism does not belong to this syndrome, for infantilism is characterized by an arrest in the general development and of the genital organs together with the non appearance of the secondary sexual characteristics. These patients do not appear like children; they look older than their age, with their wrinkles and their white hairs. The majority are of normal height. They do not belong to either the Lorain or Brissaud type of infantilism.

Myxedema is not the correct word, for these patients have not a round face, or infiltrations of the eyelids, or mental disturbances or the blood picture of the child. All that they have at the most is hypothyroidism. They do not either have Addison's disease, for in the latter disease, the melanodermia is more generalized and this syndrome is a peculiar variety of pluriglandular insufficiency.

OTHER TYPES OF PLURIGLANDULAR SYNDROMES.

1.—THYROID OVARIAN INSUFFICIENCY WITH PITUITARY SYMPTOMS.—To the symptoms of the preceding type are added those of acromegalia. Renon and his pupils, A. Delille, Monier-Vinard and Geraudel have observed similar cases with mild syndromes of acromegalia: abnormal growth, prominence of the jaws, hypertrophy of the tongue, increase in size of the hands and feet, together with headache and decrease in vision. All these symptoms are improved by thyroid and ovarian organo therapy while they are made worse by pituitary medication.

Thyroid ovarian insufficiency in a case of L. Levi coexisted with a fat dystrophy, associated with polyuria and polydypsia.

2.—A certain number of obscure syndromes are classified by certain writers among the pluriglandular syndromes. Such are: *bulbo-spinal myasthenia*, improved by ovarian pituitary organo therapy (A. Delille, Cl. Vincent).

Sclerodermia associated with:

(*a*) Melanodermia, due to thyroid ovarian insufficiency.

(*b*) Exophthalmic goitre (Raymond).

(*c*) Exophthalmic goitre and tetany (Dupre and Guillain).

(*d*) Acromegalia.

(*e*) Dercum's disease. It is, however, up to now impossible to say for sure the exact nature of these different associations.

* * * * *

The conception of pluriglandular syndromes has a practical interest: the application of mixed organo therapy in their treatment.

Renon has insisted on the successful results which may be obtained by a mixed organo therapy which would fail if only one gland was used.

As an illustration, we will recall the use of thyroid ovarian medication in ovarian insufficiency. In the same manner, thyroid and testicular extracts can be used in infantilism. It may be of interest to use the extract of one gland, whose inhibitive action is known, on a certain hypertrophied gland. It is in this manner that the pituitary decreases the thyroid secretions and that pituitary extract can be associated to the action of dethyroided animal serums in the treatment of Basedow's disease.

PATHOLOGY OF THE SYMPATHETIC SYSTEM

INTRODUCTION TO THE STUDY OF THE NERVOUS SYSTEM OF VEGETATIVE LIFE FROM AN ANATOMICAL AND PHYSIOLOGICAL POINT OF VIEW.

By A. C. Guillaume.
Interne to the Paris hospitals.

CHAPTER XIV.

THE SYMPATHETIC, CRANIO-PELVIC SYSTEM, AUTONOMIC SYSTEMS, ENDOCRINE GLANDS.

Without a clear understanding of the morphology and physiology of the sympathetic system, it is absolutely impossible to understand its pathology and still less its clinical manifestations. It is the same in this system as in the central nervous system, and we know from experience how impossible it is to study nervous diseases without at least a fair knowledge of the anatomy and physiology of the nerve centers and their peripheral dependencies.

But, while as regards the central nervous system, text books are numerous as to its physiology and anatomy, when we come to the nervous system of vegetative life there is so far no book that is really up to date on this subject.

Having for some time now studied this problem, I have condensed in one volume,[1] the facts that are available on the subject. This avoids my going into detail into certain phases of the subject which are exposed and described in this other book, and which, because of their length cannot be logically included in this work.

The plan of this chapter, because of its position in this volume, has to be more specifically adapted to the general character of the book.

In the present chapter I have primarily attempted to indicate the anatomical and physiological facts, which are absolutely necessary to the understanding of disturbances caused by changes of the sympathetic and associated systems. These disturbances are taken up in a following chapter by Dr. Harvier. I have allowed myself only to indicate the pathological changes which are directly due to anatomical or physiological facts. My object is to simplify this subject in studying it only from an anatomical and a physiological point of view, trying to describe all that is necessary to the understanding of the subject, but no more.

---

[1] Le sympathique et les systemes associés: Masson Edit. Paris, 1920.

The plan outlined is as follows:

1.—WHAT DO WE UNDERSTAND BY THE SYMPATHETIC SYSTEM?—Evolution of the various conceptions and definition of the parts.

2.—ANATOMICAL UNITY OF THE VEGETATIVE NERVOUS SYSTEM.—The neuro-organic cell and the vegetative neuron; the motor organic arc and the modes of transmission of the neurons. The sensory vegetative arc.

3.—THE VARIOUS PARTS OF THE SYSTEM.—The vegetative centres, extra axial vegetative pathways; ganglions of the vegetative nervous system.

4.—ANATOMICAL AND PHYSIOLOGICAL DESCRIPTION OF THESE SYSTEMS.—The vegetative nervous systems arising from the cerebral trunk; from the spinal column. The local visceral systems. Physiological plans of the various vegetative systems.

5.—PHYSIO-PHARMACOLOGICAL OPPOSITION OF THE TWO GREAT VEGETATIVE SYSTEMS.—Pharmacological electivity and antagonism. Pharmacology of the nervous system of vegetative life; the endocrine glands and the pharmacology of vegetative life.

I. WHAT DO WE MEAN BY THE SYMPATHETIC SYSTEM?

If we look up in a modern dictionary the definition of the sympathetic system we find that under this name have been described a bundle of nerve filaments and ganglions, which correspond fairly closely to the anatomical entity that the old anatomists described under the name of intercostal nerve or trisplanchnic nerve. This means that the general anatomical conception of this system has not changed for the last two centuries. I will even say that, as the details became better known, the general conception became more confused.

For instance, if we read the book of Jacques Benigne Winslow (1723) on "The Anatomical Exposition of the Human Body," we see that he describes, not one, but three sympathetic nerves: The greater sympathetic, the only one which is now found in modern text books, the middle sympathetic, or vagus, and the small sympathetic or the modern facial nerve.

We must remember that the "theory of the sympathetics," which was very popular at that time, made these nerves the anatomical elements necessary to the propagation of expressions, and allied conditions. If we look up the many examples of the "sympathetic" that they give, we are struck by the fact that these "sympathetic functions" belong nearly all to organic life as we understand them now. These old anatomists were therefore perfectly correct to include, as Winslow did, the vagus among the sympathetic nerves. They were perfectly right to mention the facial nerve which to a certain extent belongs to this system, as well as many other nerves which they did not suspect.

Winslow, following Petit, and about the same time Johnstone, as well as Lucas, had oriented the problem of the morphological and physiological significance of this system in an entirely different direction, in that they considered this system independent, from a physiological point of view, of the central nervous system. With the masterfulness of a genius, Xavier Bichat started the bases of our present knowledge in his two chief works: "General Anatomy"; "Researches on Life and Death."

All which, in his writings, refers to the mechanism of organic life could be quoted to-day, as well as a century ago, and would give the essential facts of the nervous regulation of the organic or vegetative organism.

Knowing already the difference between the two processes: vegetative and organic life, Bichat shows that the anatomical system of "the ganglia" presides on the first, while the latter is commanded by the cerebro spinal axis and its dependent nerves. This statement is really too absolute; nevertheless, it is pretty nearly correct and had a certain amount of influence on the subject.

"So far all the anatomists have considered the nervous system as a uniform system, but one has only to think of the various methods of distribution, the texture, the various properties and uses of the various branches to see that it must be divided into two general systems, essentially distinct of each other and having for chief centres, one, the brain and its dependencies, the other, the ganglia. The first belongs primarily to animal life. It is the agent of transmission to the brain of exterior impressions which become sensations and also serves as conductor to the will of this organ, which is executed by the voluntary movements. The second, nearly everywhere distributed to the organs of digestion, circulation, respiration and secretion depends more particularly to the vegetative life, where it has a more obscure part than in the preceding. Neither is limited strictly to the organ of one or the other life, for instance; certain cranial nerves send filaments to glands, to involuntary muscles, etc., and the nervous system of the ganglia has sometimes filaments in voluntary muscles. It is by the general disposition, leaving aside the few exceptions, that the division of these two systems is based. No parallel is made here to show the difference, for the exposition of each is all that is necessary to convince of the difference."

Certainly the arguments of Bichat, which try to prove an animal symmetry and a vegetative symmetry seem childish to us, nowadays, since histology and embryology have shown us that primarily these various textures are symmetrical whether belonging to the animal or to the vegetative system. But in enumerating the tissues of the vegetative system, in order to prove their symmetry, Bichat gave a fairly accurate classification of the tissues of vegetative life. As regards the general significance of these two lives and their mechanism, Bichat leaves very little to be said.

"It seems as if the vegetative is the sketch, the canvas of the animal, and to complete it, it has been necessary to cover this canvas with an apparatus of external organs, suitable to establish relations. From this result two distinct animal functions. Some consist of routine successions of assimilations and excretions by which changes occur in its own body of neighboring molecules and the injection of these molecules. By this function it lives only in itself, by the other it exists outside of itself. The animal is a dweller of the world and not like the plant of the spot where it was born. It feels and sees what surrounds it, thinks of its sensations, moves voluntarily and often can communicate by means of the voice its desires, fears, pleasures and sorrows.

I call vegetative life the functions of the first group, because all organic things, vegetable or animal, show it to a more or less degree and an organic texture is all that is necessary to its function. The various functions found in the second group make up animal life, so called because it is only to be found in the animal kingdom."

A last point deserves to be brought up.

What does Bichat understand by the nervous system of vegetative life?

"No anatomist has ever considered the nervous system of the ganglia from the point of view under which I will present it. This point of view consists in considering each ganglion as a centre, independent of the others in its action, furnishing and receiving its nerves, as does the brain and having nothing in common by anastomosis, with other analogous organs, so that there is a remarkable difference between the animal and vegetative nervous system, in that the first has a single centre in the brain, which is reached by all kind of sensations and from which arise all kind of impulses, while in the second there are a number of centres and therefore as many nervous systems as there are ganglia. From the general conception which I have given of the ganglia, it is evident that this nerve, (the greater sympathetic) does not really exist and that the continuous structure that is to be found from the neck down to the pelvis is really only a series of nerve communications, a series of anastomosis sent out by the various ganglia and not a nerve starting from the brain or the spinal cord.

"It seems to me that most anatomists have a very erroneous idea of this very important nerve.

"They all represent it as a medullary filament, from the head to the sacral region and sending out throughout its course branches to the neck, chest and abdomen, following in its distribution a course analogous to the spinal nerves and arising, according to some, from these nerves, or according to others, from the brain. Whatever name it be given, be it sympathetic, intercostal, trisplanchnic, etc., the way of looking at it is always the same.

"I think this view is entirely erroneous and that such a nerve does not exist and what is taken for a nerve is a series of communications between nerve centres.

"These nerve centres are the ganglia. Scattered over various regions of the body, they have an isolated and independent action. Each is a focus sending out a number of branches carrying to certain organs the impulses from the focus from which they arise. Among these branches, some go from one ganglion to the other and as these branches together look like a continuous structure, this structure has been considered as one nerve. These branches are simply anastomosis and not a nerve in itself.

"From now on, I will divide my descriptions of the nerves into two great systems. One arising from the brain, the other from the ganglia. The first has a single centre, the other a multitude. I will first examine the divisions of the central nervous system; afterwards I will take up the system of the ganglia which can be divided into those of the neck, head, thorax, abdomen and pelvis.

"In the head we find the lenticular ganglion, Meckel's ganglion, that of the sublingual gland, etc. In spite of the fact that no communication exists between these centres, either among themselves or to the so-called greater sympathetic, their description belongs to the latter since these communications are only accessories to this system of nerves. In the neck, the three cervical ganglia and sometimes one other, on the side of the tracheal artery; in the chest the twelve thoracic; in the abdomen the semi lunar and lumbar ganglia, etc.; in the pelvis the sacral ganglia, these are the different centres to which are attached a number of branches which have to be examined separately as we examine the cerebro spinal system. In the same manner in the neck and the head, each ganglion will be described, then its branches will be taken up. As the ganglia of the chest, the lumbar region and pelvis have a very similar disposition, the description will be more general for each region.

"This way of looking at the nerves by demarking the great difference between the great nervous systems, present these systems as they really are in nature.

"What anatomist has not been struck by the difference to be found between the nerves of one or the other. Those of the brain are larger, less numerous, whiter, more dense in their tissue, less liable to changes. In opposition to this those of the ganglia are very loose, numerous, particularly around the various plexuses, gray in color, soft and varying in appearance, except those communicating with the cranial nerves and those uniting together these small nerve centres.

"It is evident after these considerations that there does not exist a greater sympathetic nerve, and what is described under that name is really a number of small nervous systems, functioning isolately, but having communicating branches with each other."

These are the essential facts of the theory of Bichat on the system of the ganglia and their application on the nerve mechanism of vegetative life. If I have insisted so much on these theories, and if I have quoted so extensively his original writings, it is that I believe that to-day, as well as a century ago, these paragraphs, taken from Bichat's masterpiece are still valuable knowledge. To-day as in the past, his conception of the greater sympathetic, barring out a few details, is still what we consider nowadays to be the truth. Certainly details have to be corrected, in particular the independence of the two systems, animal and vegetative, and we must give back to the cerebro spinal system a certain amount of control over vegetative life. Certainly we have to add considerably to reach our modern conception, but these additions are really more in the physiology than in the anatomy of the subject. As Blandin says, "It is only fair to say that no one has attached so much importance to this idea and upheld it with more intelligence." I will add that I consider Bichat's theories as the basis of the modern conception of the nervous regulation of vegetative life. Practically speaking this conception is found in the writings of Bichat—all that is necessary is to make a few corrections.

CORRECTIONS TO BE MADE ON THE THEORIES OF BICHAT.

Following the guiding idea, that is, the exposition of the historical facts which lead to our present day knowledge of the vegetative nervous systems, I will now indicate the changes that have been found necessary.

Bichat believed in the independence of the two systems; in that respect he was wrong, for while it was a good thing to show this independence, more relative than real, we must not lose view of the fact that in reality the cerebro spinal system contains both centres of the vegetative and animal life and in the same manner Bichat exaggerated the relative autonomy of the ganglionic centres.

Another point, Bichat is very indefinite in the classification of the ganglionic nervous systems which make up the sum total of the vegetative nervous system. It is necessary to say, as did Winslow, that the vagus belongs mostly to the vegetative life.

This said, let us repeat that Bichat's works are to be considered more as an outline than a complete description. Bichat died young, and in justice's sake we must say that his theories stayed and that they were the starting point of our modern conceptions. After him we must go to Claude Bernard, then to the modern Russian and English schools of physiology to find anything which shows any equivalent improvement.

THE ADDITIONS OF MODERN ANATOMY AND PHYSIOLOGY.

With Claude Bernard, the physiological action of the vegetative nerves was made more precise, and the physiological and biological significance of these systems became evident. Claude Bernard showed the action of the sympathetic in the regulation of the vegetative processes, secretions, vaso-motors, heat regulating mechanism, etc.

Finally, English physiologists, Langley and Gaskell in particular, after adding to the work of Claude Bernard and his successors a number of essential facts, after having shown the importance of the electivity of reactions of the vegetative system to organic substances, established a new theory in which an enlarged vegetative system, more definite in its physiopharmacological details is put in value as to its physiopharmacological antagonism and its physiological relation to the glands of internal secretion. There are therefore three periods in the study of the vegetative system.

An initial period chiefly morphological, that of Winslow, Johnstone and Bichat.

A physiological period, J. Mueller, Claude Bernard.

A physiochemical period, the work of the English school.

The evolution of the theory in time, will be the plan followed for the evolution of thought, corrected of errors and wrong conceptions, in all things should be considered as the best way to expose a plan.

At the end of this first chapter let us conclude that to have a definition of the nervous system of the vegetative life, as shown by Bichat and others, we must insist that the body contains two distinct systems: An animal life system, cerebro spinal axis, and nerves. A vegetative life system, system of ganglia.

We must show: That these systems have their centres superimposed, in the nervous axis except for a few exceptions and are themselves controlled by higher centres which are to be found in the anterior portion of the brain in the neighborhood of the higher psychic centres; that the nerves coming from the vegetative axis centres have for particularity to be interrupted, in ganglia outside these centres; finally that the nerves of the vegetative life are throughout the organism, distributed in a series of tissues which have to do with the upkeep of the individual and the species. These are the main facts. Let us now see, how these systems are planned and how they function.

II. THE ANATOMICAL VEGETATIVE NERVOUS UNITY.

Before going into the description of these systems, we must analyze the various parts and describe successively, the vegetative nerve cell, the vegetative neuron and the vegetative arc.

THE VEGETATIVE NERVE CELL AND THE VEGETATIVE NEURONS.

Do vegetative nerve cells distinguish themselves from the neurons of animal life? Certainly, for one thing the central and ganglionic vegetative cells are slightly different from the nerve cells of animal life and furthermore, the axis cylinder of these cells have an entirely different aspect.

I don't want to enter here into a histological description of the comparative characters of these two types of neurons; all that I will say is that the vegetative fibres are of two kinds:

AMYELINIC Fibres without a myelin coat of *Remak*, or gray fibres and vegetative with myelin fibers whose chief characteristic is the extreme smallness of their diameter as compared to those of the animal system.

More important from a clinical point of view is the grouping of the neurons into functional arcs.

THE FUNCTIONAL VEGETATIVE MOTOR ARC.[2]

Let us take, if you wish, a motor cell of the vegetative central axis, a vegetative motor cell, situated in one of the medullary segments or one of the middle or posterior lobes. Let us say that this cell is located in the lateral portion of the anterior horn (intermedio-lateral tracts). From this cell will arise an axone, a vegetative fibre with myelin, which reaches the anterior root of a spinal nerve, then follows this nerve up to the sympathetic ganglion of the lateral chain. Leaving then the mixed nerve and following the vegetative fibre, the vegetative ganglion is reached. When this is reached—in the simplest case—this fibre articulates with a vegetative ganglionic cell. That is, the nerve endings communicate with the ends of the ganglionic cell. From this cell arises a gray ramus, which, leaving the ganglion, goes, either towards a visceral cavity of the organism, or to the periphery, by following again the spinal nerve. In the first case, the visceral nerve reaches the vegetative tissues of the viscera; in the second case, it unites to the spinal nerve to distribute itself to somatic tissues of the periphery, following the distribution of the latter; we must note, however, that certain of these fibres abandon the spinal nerve and its branches, to follow up the spinal nerve, and reach in this way the vegetative tissues of the meninges. This done, we can now classify these fibres and give them a name. First of all let us name the white fibre which joins the vegetative central axial cell, with the ganglionic cell.

---

[2] For a better understanding of this paragraph see Figs. 20, 22, 23.

This fibre is called the *pre-ganglionic* or *precellular fibre.* I myself call it *central ganglionic fibre.* The name we give to the gray fibre which arises from the ganglionic cell is *post ganglionic* or *post cellular* fibre; for my part I prefer to call it vegetative ganglionic fibre, and, I think that we should differentiate the fibres of this last group into those that reach the vegetative tissues of the periphery and those that are distributed to the vegetative tissues of the splanchnic cavities. I have grouped under the name of vegetative ganglionic fibres on one side the fibres going to the periphery or ganglion-somatic fibers and on the other the fibres destined to the splanchnic area or ganglion-splanchnic fibres.

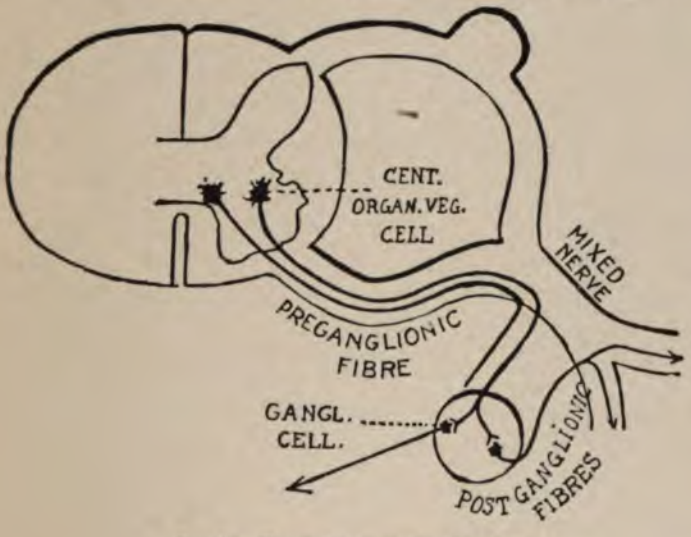
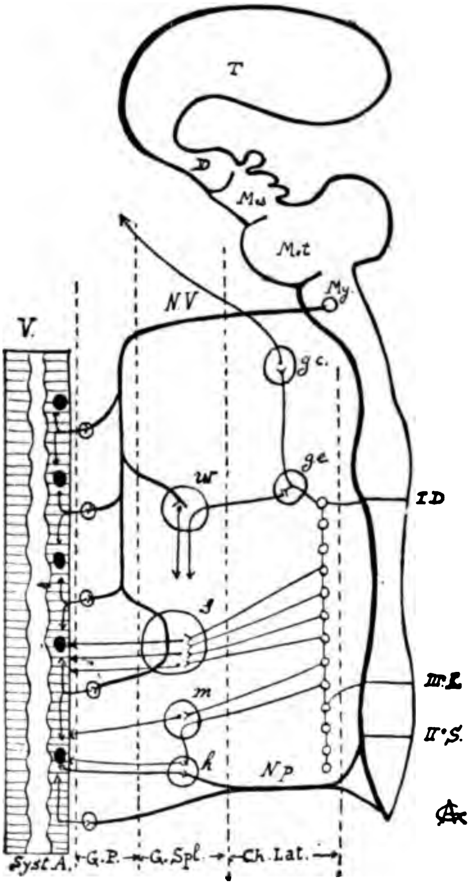


Fig. 20.—Vegetative motor functional arc.

This is the most simple motor vegetative functional arc; this is the type that is followed always by the ganglion —somatic distribution, but there are other modifications which are united in various combinations with the central ganglionic fibres.

ENDING OF THE CENTRAL-GANGLIONIC FIBRE.

What we are about to study now only applies to the ganglion-splanchnic distribution. This must be remembered, as many fibres do not terminate in the nearest ganglion of the central axis; many simply go through it to reach a more distant ganglion. These last-named ganglia can be, according to their distribution, divided into two groups:



This diagram shows the grouping of the various systems of ganglia. The vertical dotted lines show the separation of these several groups; Lateral chain ganglia grouping (Ch. Lat.); large splanchnic median plexus ganglia group (G. splanch) finally visceral autonomous ganglia groups (Syst. A.).

To the right of the drawing is a drawing of the central nervous system, at its superior portion the 5 cerebral lobes: "T" designating the telencephalus, "D" the Diencephalus, "Me" the metencephalus, "My" the Myencephalus. At the inferior portion are shown the lines I, D, III, L, II, S which indicate the dorsal, lumbar and sacral regions. To the left is a diagramatic drawing of the intestinal tract.

FIG. 21.—The ganglionic group: V. viscera; N.V. vagus; N.p. pelvic nerve; w.g. of Wrisberg; s. solar ganglia; m. mesenteric; g.h. hypogastric ganglia; g.c. sup. Cervival; g.g.e. Stelar ganglion.

1.—A group of ganglia situated outside of the lateral chain and which do not give rise to any ganglion somatic fibres. These ganglia are characterized by the fact that they are located outside the viscera.

2.—A group of ganglia similar to the former, but which are inside the viscera.

The first group are called *splanchnic ganglia*, and most of these ganglia are located in the median sagital plane of the body. The second group are called intra-visceral ganglia or parenchymatous ganglia.

How do the central ganglionic fibres end in these ganglia? Certain central-ganglionic fibres travel with the ganglion splanchnic fibres, arising from the lateral column or lateral vertebral ganglia and with them, reach the splanchnic ganglia where they end as did the fibres of the first type, by communicating with a ganglionic cell, from which arises a ganglion-splanchnic fibre. Other central ganglionic fibres go further and reach the parenchymatous ganglia, where they communicate with a ganglionic cell; from this cell will arise the splanchnic-ganglionic neuron. Therefore should we look at the central ganglionic-fibres and the ganglion-splanchnic fibres we see that according to their endings in successive ganglia, the fibers which reach these ganglia get longer and longer and inversely the ganglion-splanchnic fibers are respectively shorter and shorter.

VARIATIONS OF ENDINGS AND COMMISSUREAL FIBRES.

Proceeding always from the simple to the more complex, I will now describe the variations of endings in the different ganglia of the various successive groups of ganglia, then I will describe the commissureal fibres which unite the ganglia of the lateral vertebral column to each other.

I have said that the central ganglionic fibre ended: *en block*, in a ganglion of one of the groups of ganglia, and from this ganglion arises a second relay. In reality a central ganglionic fibre may, by the collaterals which it gives off, give birth to ganglion-splanchnic fibres, in several ganglia. In this way it may give birth to ganglion-splanchnic fibres in successive ganglia of various groups of

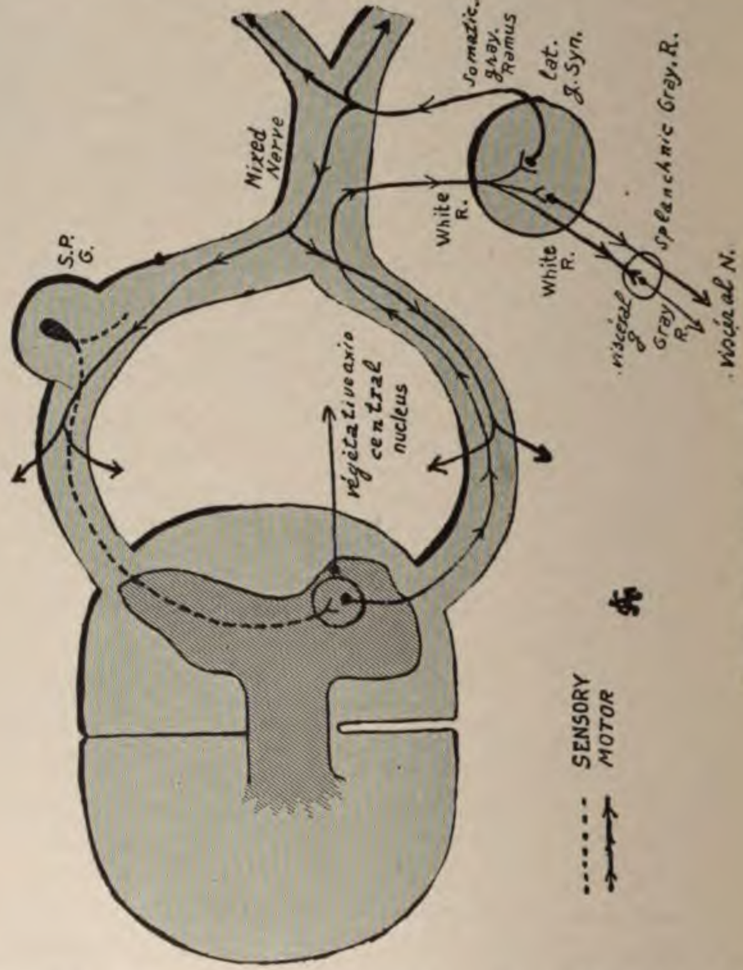


FIG. 22.—The various elements of the motor arc.

ganglia and in other cases (in the lateral chain only), a single central ganglionic fibre will give birth to successive ganglion-splanchnic fibres which will branch out at various levels in the lateral chain. In this way, both in length and in height, the disposition becomes more complicated. Furthermore, we must know that in height, next to giving off of successive collaterals, which after interruption communicate with ganglion-splanchnic fibres, there exists also a change of plane *en block* of the central ganglionic fibres. In this way a central ganglionic system gives off sometimes ganglion-splanchnic fibres, sometimes ganglion-somatic fibres. Fibres, which if looked at as a whole, can arise from a lower plane to the original plane of the central ganglionic group. There is, therefore, a change of level from the top and one from the bottom. We shall see that as far as the thoracic and lumbar region is concerned this change of level is not due to chance.

Finally, and this is an important point, there exists in the lateral chain commissural fibres which unite the various ganglionic centres of the lateral chain.

This complex structure is found in all superior vertebrated animals. Comparative anatomy reveals that the inferior vertebrates have a much simpler sympathetic system; the lateral chain only exists as isolated ganglia, separated from each other. Furthermore, let us not forget that this abnormal disposition may also be present in man as shown by Bichat and that we have spaces between the various portions of the lateral column.

Here then in general is the disposition of the motor arc. Notice that the motor arc has two neurons: one extra axial neuron, the vegetative central ganglionic neuron, and the ganglion-splanchnic or ganglion-somatic neuron.

THE VEGETATIVE SENSORY ARC.

Do real vegetative sensory tracts exist, and if so, are these anatomically different from the animal sensory tracts? If we are guided by physiopathological facts of laboratory and clinical observation, we are tempted to believe so, for we are in the habit of considering that there is a visceral sensation, absolutely different in its responses to the excitations of the animal system. Certain anatomists, Dogiel particularly, have even described particular anatomical dispositions, which in the spinal ganglion assures the connection between the vegetative sensory tracts and the animal sensory tracts, and would thus explain certain physioclinical manifestations. In reality, it is not necessary to have a special anatomical disposition to explain the physiological differences between the two great types of sensation stimuli; vegetative stimulus, unconscious under physiological conditions, and conscious animal stimulus. I have in some other[3] part of this book explained the facts which allow us to conclude that:

1.—Vegetative sensation is subject to the same general laws as the various animal sensations.

2.—The differences observed in physiology, and in clinical pathology are not due to special anatomical dispositions, but are united to the condition of the excitation from the point of view of its quality.

3.—When all is said, vegetative sensation reacts unconsciously to ordinary stimulation.

4.—That in one, as well as in the other great system, an ordinary stimulation, as to quality, but extraordinary as to quantity, will cause a sensation of pain.

---

[3] The sympathetic and associated systems.

THERE ARE NO PARTICULAR ANATOMICAL SENSORY VEGETATIVE TRACTS IN THE VEGETATIVE SYSTEM. THERE ARE ONLY DIFFERENT DEGREES OF STIMULATIONS.

This explains all the physiopathological phenomena of vegetative sensation. We know for instance, and we will understand why it is that the intestines can be cut without pain, while pain will be severe if the intestines are distended, pulled or stimulated by a chemical agent, either acid or base.

The explanation is easy. As long as we do not enter the field of ordinary stimulation to which the vegetative tissue is accustomed, these tissues do not respond, just as in life we do not salute somebody we do not know.

Another example: Let us stimulate a vegetative tissue, using one of its usual stimuli, and to use a more concrete example, let us say that we stimulate the intestinal mucosa with a small quantity of an acid or a base. We will then notice, that as long as we stay within the usual limits of intensity, the only response will be motor or secretory, without any conscious sensation.

As in the previous case, the explanation is easy. As long as we stay within the quantity limits of usual stimuli only motor or secretory reflects are produced.

Finally let us again stimulate vegetative tissue with a strong chemical reagent. On top of the motor and secretory reflex we will find that a pain sensation will appear; this means that the exaggeration in quantity of the stimulus is a pathological condition, and is the cause of the pathological sensation of pain.

It is not, therefore, necessary to suggest the presence of a gastric ulceration to explain pain due to hyperchlorhydria, simple hyperacidity is sufficient; the same theory of origin of visceral sensation will explain the origin of pain, in patients who, for a therapeutic purpose, abuse of alkaline medications.

Let us come back to the physioanatomical facts. We

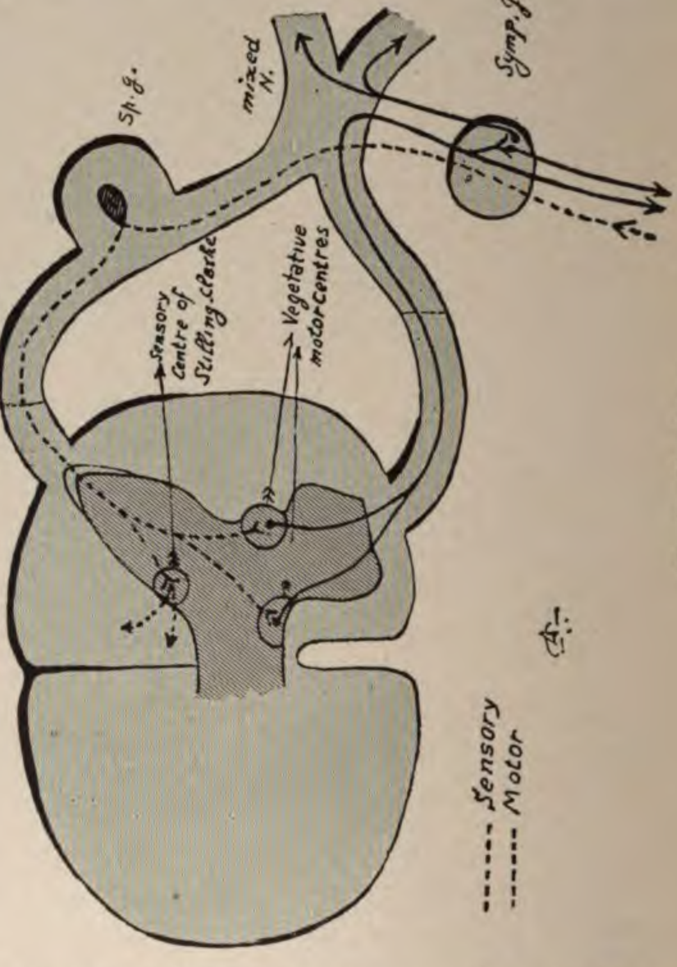


FIG. 23.—The reflex arc.

have just seen that vegetative sensation does not need special fibres, united to the sensory fibres of the cerebro spinal axis, to explain the peculiarities of the sensations of the vegetative life; this does not mean, however, that there are no sensory vegetative tracts, viscero-sensory in particular, in other words, afferent vegetative tracts. These tracts exist, but they are no different from those of the animal system and one is led to conclude, that only in a certain measure does the motor stimulant part of the nervous system of the vegetative life, distinguish itself anatomically from the corresponding part of the system of animal life.

Let us now follow the sensory vegetative fibres. These fibres coming from the viscera and vegetative tissues in general, reach, after following the general course of the motor tracts, the spinal ganglion and from there, divide themselves, as do the sensory fibres of the voluntary system; that is, there are direct segmentary tracts, tracts which will connect with the motor, central vegetative cells (this is the road taken by the impulse of the unisegmentary vegetative reflex); and there are also pluri-segmentary tracts as in the voluntary system (tracts which are the cause of vegetative reflexes in different planes) and long tracts which reach the superior centres of the animal system.

In this distribution of the pluri-segmentary and long tracts, a group of cells of the posterior horn play an important part, these are part of the cells *of the column of Stilling-Clarke;* it is apparently the group of cells which play the part of sensory distributors, as the neighboring cells of this same group play the parts in the territory of animal life.

With the study of the sensory tracts of the vegetative system and their axis nerve centres, we have completed the description of the unit composing the vegetative arc. We have analyzed the parts; let us now, following a logical sequence, study the details of these systems.

III. THE COMPONENTS OF THESE SYSTEMS.

What are the various anatomical and physiological components of these systems?

This is the question which we are now going to study.

We must in the vegetative, as well as in the other system, describe:

1.—Higher centres.

2.—Spinal centres.

3.—Peripheral nerve fibres and, this is particular to the vegetative system.

4.—Ganglia interrupting the motor tracts.

THE HIGHER CENTRES OF VEGETATIVE LIFE.

As I have shown previously and as it occurs in the animal system, these higher centres are located in the anterior lobe, which, as we know, is divided into two parts.

Telencephalus—Hemispheres.

Diencephalus or thalamencephalus—optic layer.

It is both in the cerebral hemispheres and in the optic layers that we must look for these centres. They are superimposed to the animal centres, but their exact location is not yet exactly determined. What is certain, however, is that, from a physiological point of view, and speaking very generally, the cortex and the medulla contain centres which when stimulated react on the vegetative system. From these centres arise fibres destined to reach the spine and which pass through the internal capsule, as do the fibres of the voluntary system. Needless to say, that in the cortex also end the long sensory fibres of the vegetative system. From this we may conclude that: the higher centres of the anterior lobes contain both centres of the voluntary and involuntary nervous systems. These centres are physiologically and pathologically interdependent and influence each other. As regards the animal system, the higher vegetative centres do not necessarily enter in the various processes, and I will even say, that as far as the vegetative system is concerned, the intervention of these centres is uncommon. These centres are not indispensable, but pathologically they may become prominent and the intervention of the psychic or psycho motor centres play an important part in disturbances of the vegetative life.

THE SPINAL CENTRES OF THE VEGETATIVE SYSTEM.

These centres are located in the spinal cord and can be divided into two groups.

1.—Motor centres. 2.—Sensory centres.

MOTOR CENTRES.

These centres are located in the lateral posterior portion of the anterior horn of the cord, or its equivalent. Let us add, that in certain regions of the axis exist other vegetative cell groups, located on the median ventral part of the anterior horn, in the neighborhood of the commissure; it is, therefore, these two groups of cells that we are going to investigate.

A. CELLULAR GROUPING OF THE CEREBRAL TRUNK.

These groups are in the cerebral peduncle and in the bulb.

In the *cerebral peduncle*, the vegetative nucleus formed by the anterior and dorsal nuclei of the *oculo motor* (III cranial), which is located on the floor of the aqueduct of Sylvius. It is the pupillary nucleus.

In the *bulb* are found 5 vegetative nuclei; they are:

(*a*) Juxta-pretuberantial nucleus, located in the median side of the nucleus of the facial nerve. It is the lacrymal nucleus, which I prefer to call *lacrymal mucous facial nucleus.*

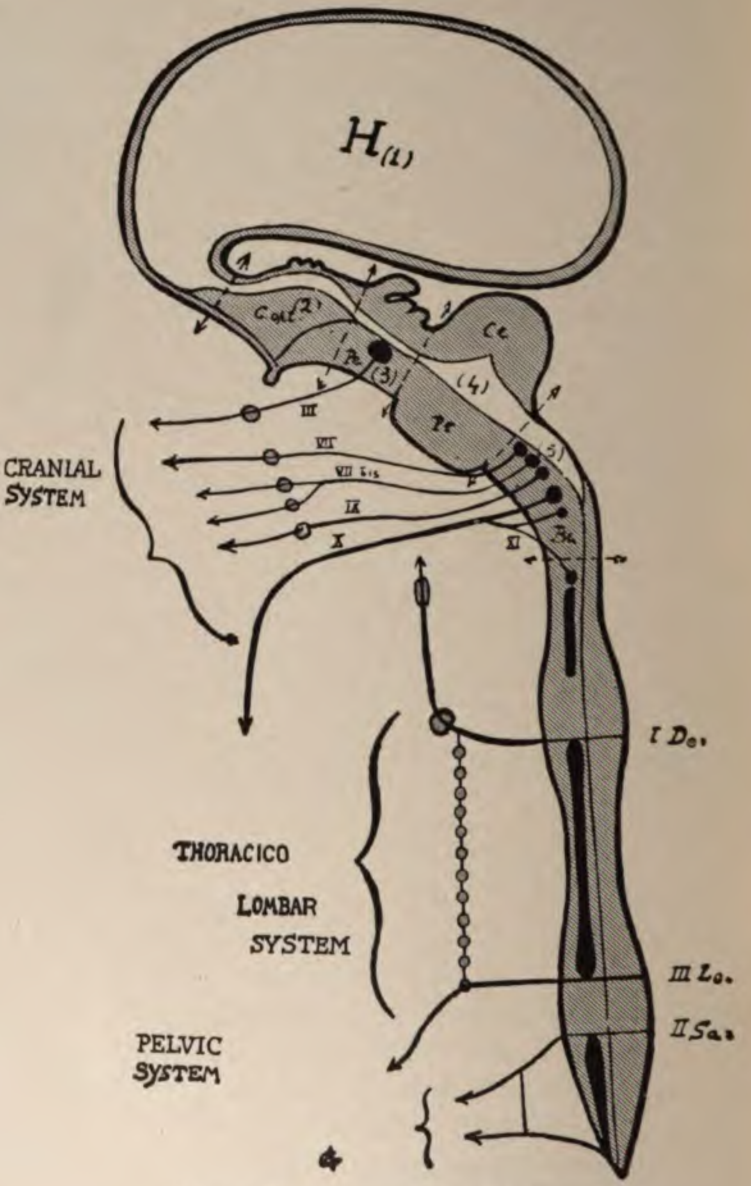


FIG. 24.—Vegetative nervous system as a whole.

(*b*) Juxta pretuberantial nucleus located dorsally to the preceding one. It is the superior salivary nucleus.

(*c*) The superior bulbar nucleus, located in the neighborhood of the motor nucleus of the glossopharyngeal (IX cranial nerve); this is the inferior salivary nucleus.

(*d*) Middle bulbar nucleus, located between the motor nucleus of the vagus and its sensory nucleus (solitary nucleus). This is the *dorsal nucleus of the vagus* or *vegetative motor nucleus of the vagus;* to the vegetative nucleus of the vagus we must also add:

(*e*) The vegetative bulbar nucleus of the XI cranial nerve, and its medullary vegetative nucleus, for this nucleus brings to the vagus vegetative fibres. Finally, we must describe:

(*f*) A vegetative bulbar nucleus, probably of the hypoglossal (XII cranial):

It is believed by some that there exist also one or more vegetative nuclei annexed to the V nerve. In reality, in spite of the fact that this is not settled, it probably is not so; for we shall see that the vegetative fibres which follow the V, only follow it part of the way and cannot be attached to the nerve, as was the case of the preceding vegetative nucleus.

B. CELLULAR GROUPING IN THE SPINE.

We must study separately: the cellular groups derived from the intermediate lateral part of the anterior horn and the groups derived from the medial ventral part of this same horn.

(*a*) Groups derived from the intermediate lateral zone.

They are found in three parts of the cord.

Cervical region (from the I to the IV segment inclusive).

Thoracic-lumbar region (from the I dorsal segment inclusive to the III, or IV lumbar segment).

Sacro coccygeal region (Below the II sacral segment).

They, therefore, form a column divided into three segments.

Cervical segment.

Thoracic-lumbar segment.

Sacral coccygeal segment.

Between these three segments are two interrupted zones located between the IV cervical segment, and I dorsal segment and between the III—IV lumbar segment, and II sacral segment.

We notice that these zones of interruption correspond to the root of the limbs, and that the intermediary segments correspond to the intermediary zones, above and below these roots. These facts are extremely important; this distribution of the nerve roots shows that in the roots which correspond to the nerve distribution of the limbs, there is, so to speak, no participation to the enervation of the trunk. There is, therefore, no question that these roots do not participate in the vegetative visceral enervation and we understand how these vegetative spinal groups become so small that they nearly disappear in these regions.

(*b*) Groups derived from the medial ventral marginal zone.

They form, as far as our present knowledge goes, a column starting below the IV lumbar segment.

SENSORY CENTRES.

I have shown that certain of the nuclei (dorsal) of *Stilling-Clarke* play a part in the distribution of sensory tracts arising from organic tissues. It is in the anterior portion of the dorsal or internal part of the posterior horn that we must look for the nuclei of the vegetative system. From the point of view of their disposition in height, we can say that these nuclei form a continuous column located between the VII—VIII cervical segment, above, and the I—II lumbar segment below. Above and below, they do not form a column, but leave indications of one in the shape of *scattered cells of Sterling Clarke.*

THE PERIPHERAL NERVE FIBRES OF THE VEGETATIVE SYSTEM.

We have seen, when we studied the various elements of the vegetative motor arc, that among these elements, there was a white central ganglionic fibre, whose vegetative cell was intra-axial, and whose axion united the central axial cell with the extra axial ganglionic cell. Furthermore, we have seen that in the cerebro spinal axis, there exist vegetative cellular groups, divided into several nuclei in the spinal column, more or less regularly placed in a column. We can now trace the bond of union between these two parts and say that the nuclei and columns correspond to the groups of cells which originate the central ganglionic fibres. As a sequel to this *the vegetative central ganglionic fibres emerge from the spinal axis by segmentary nerves which on the whole correspond to the topographic segmentation of the vegetative cellular grouping.*

This is why in the cerebral part, we see arising from the various vegetative motor nuclei, vegetative fibres which, to reach the tissues they supply, follow the course of certain nerves which arise from this part of the nervous axis. From the pupillary nucleus arise vegetative fibres which travel with the III cranial nerve; from the lacrymal mucus-facial nucleus, fibres annexed to the VII; from the superior salivary nucleus, fibers annexed to the intermediate nerve of Wrisberg; from the inferior salivary nucleus, fibres annexed to the IX cranial nerve (glossopharyngeal); from the nucleus of the vagus, the greater part of the fibres constituting this nerve (Xth); from the nuclei of the musculo spinal, fibres which go with the preceding nerve; finally from the organic nucleus of the hypoglossus, arise fibres which follow this nerve (XII cranial).

In the cervical region, the vegetative column, gives birth to fibres which follow the course of the musculo spinal fibres which we have just said, reach the vagus.

In the thoracic and lumbar region the organic column gives birth to fibres which go out in segments with the mixed spinal nerves arising between the I dorsal and III lumbar. These vegetative fibres are the white rami communicantes of the sympathetic and do not exist in any other region.

In the sacral region a certain amount of vagueness exists as to the exact part played by the two columns: the median ventral column and the intermediate lateral column. One fact, however, is definite and that is that some sacral segments, chiefly those of the II, III, IV segments, give birth to vegetative fibres which constitute the *erector plexus* (it is best because of its very general functions to call it the vegetative pelvic plexus). Outside of this fact, what is the relative importance of the median ventral column and the intermediate lateral column in the constitution of the pelvic plexus? Logically, we are led to believe that the intermedio lateral column gives to the pelvic plexus analogous fibres to those which they give off at the cervical portion and which are incorporated with the vagus; fibres which in the lumbar and thoracic part, reach both the lateral ganglia and those further located. Such are the anatomical facts. From a physiological point of view, we shall soon see that the vegetative fibres issued from the intermediate lateral column in the cervical, and the thoracic and lumbar region have different functions, sometimes antagonistic to those vegetative fibres which follow the course of the cranial nerves. We, furthermore, will see that the pelvic plexus, in a great many ways, has physiological properties very similar to the vegetative cranial nerves, but that it also possesses a series of functions similar to the lumbar and thoracic sympathetic. We are, therefore, tempted to reach the following conclusions: The median ventral column probably gives to the pelvic plexus fibres which resemble the vegetative fibres of the cranial nerves,[4] the intermediate lateral column probably gives to this same plexus fibres which physiologically resemble the thoracic and lumbar sympathetics. This is only a theory and needs to be proved by morphological and physiological facts. From a clinical point of view, however, it is not necessary to understand the respective part played by these two columns.

We have now to study the vegetative ganglia.

THE GANGLIA OF THE VEGETATIVE NERVOUS SYSTEM.

The ganglia have for a long time been considered as the chief anatomical characteristic of the vegetative nervous system. If we leave out the spinal ganglia and their equivalents in the cranial nerves (Gasserian ganglion of the V, geniculated ganglion of the VII, jugular and plexiform of the X, ganglia of Andersch and Ehrenritter of the IX, ganglia of Corti, of Boettcher of the VIII). This conception is perfectly true, but we must not consider that the sympathetic system and the vegetative nervous system are the same.

When we studied the vegetative arc, we saw that the ganglia were arranged, some as a series of beads (lateral vertebral chain), the others irregularly disposed behind the viscera (splanchnic ganglia), finally others were located in the viscera themselves (parenchymatous ganglia).

---

[4] This disposition is confirmed by the medullary localization of the defecation centre in the lower lumbar region.

Keeping this fact in mind, as we study the ganglia of the vegetative nervous system, we will bring back this classification to the general topography of the fibres arising from the cerebro spinal axis.

Let us classify first the ganglia of the lateral chain, that is to say, the ganglia located on either side of the cord and united to each other by nerve fibres, from the superior cervical ganglion (I, II cervical vertebra), to the coccygeal ganglion (coccyx). All these ganglia, depend on fibres arising from the vegetative thoracic-lumbar medullary column. In these ganglia we find two different groups. One which controls the vegetative ganglion-somatic fibres, one which controls the ganglion-splanchnic fibres. Each ganglion of the lateral chain is, therefore, composed of a somatic and a splanchnic part.

As regards the cranial nerves of the vegetative system, which include all ganglia outside of the spinal ganglia arising from the spinal nerves, we must differentiate between true ganglia (the centre of a ganglionic cell, interruption of an arc) and ganglioniform masses (crossing or knot of fibres). Only the true ganglia are going to be studied, as the ganglioniform masses are really only anatomical peculiarities. In the head, the vegetative ganglia up to now have always been connected with the sympathetic. This is not correct, if, as so often is the case in text books on anatomy, we fail to recognize a vegetative system, of which the sympathetic is only one of the parts. The vegetative cranial ganglia are as many different elements belonging to different vegetative systems. These ganglia are: The ophthalmic ganglion, the sphenopalatin ganglion or of Meckel, the optic ganglion or of Arnold, the submaxillary, maxillary or lingual, which seems to be related to the inconstant sublingual ganglion described by Blandin; finally, the ganglion of Langley.

All these ganglia belonging to the cranial portion of the vegetative system are grouped in the following manner: The ophthalmic ganglion is connected to the vegetative system of the oculo motor; the spheno-palatin ganglion to the vegetative system of the facial; the maxillary ganglion and the ganglion of Langley to the vegetative system of the intermediary nerve of Wrisberg; the optic ganglion to the vegetative system of the glosso-pharyngeal.

Outside of these ganglion, there are only ganglioniform masses without any physiological interest, and furthermore, contrary to what is generally believed, they have only unapparent connections with the thoracic lumbar sympathetic; in other words, the sympathetic fibres do not stop in the vegetative cranial ganglia; they simply go through them, as opposed to the cranial vegetative fibres which do stop. These facts result from the experimental work done by English physiologists on nicotine.

As for the splanchnic ganglia of the thorax, abdomen and pelvis, cardiac ganglionic plexus of Wrisberg; solar plexus (semi lunar, superior mesenteric and renal ganglia); inferior mesenteric plexus (inferior mesenteric and hypogastric ganglia), they do not belong as a whole to one vegetative system, but anatomy and physiology show us that they are more or less connected with the vegetative tracts arising from the spinal axis.

Anatomically the sympathetic thoracic, the vagus and finally the pelvic give off fibres to these ganglia. This means that these ganglia are physiologically connected with the various vegetative systems. To be more precise, now that we know the value of these vegetative ganglia, is there an interruption of the fibres of these various systems in the ganglionic cells of these ganglionic plexuses?

This question can be answered, but each ganglionic plexus must be examined separately.

As far as the cardiac ganglionic plexus is concerned, the fibres arising from the thoracic and lumbar region of the vegetative centres, only go through the ganglia without stopping. *All the fibres which end there come from the vagus.* The ganglion of Wrisberg must therefore, physiologically belong to the vagus and not to the sympathetic.

As regards the solar plexus, it seems here to be the reverse and that it *belongs entirely to the sympathetic,* the vagus goes through it without stopping. It must, therefore, be considered as part of the sympathetic.

Finally, as regards the inferior mesenteric plexus and its dependency the hypogastric plexus, they are chiefly part of the sympathetic system. At best the pelvic plexus has a few endings in certain visceral ganglia which depend on the hypogastric plexus.

We have now to classify the visceral or parenchymatous ganglia. These ganglia are found located against, or in the walls of the viscera; lung, digestive tube, heart, urinary system, genital system, even possibly in the wall of the blood vessels.

They are much more difficult to classify than the preceding ones. It seems, as do the splanchnic ganglia, that they are not composed of one type. It appears as if there were:

1.—Ganglia belonging to and depending on the vegetative nerve axis.

2.—Ganglia, physiologically autonomous, which could be affected and commanded by the fibres coming from the nerve axis, but for a certain length of time, these systems can function alone.

In the first group we must include certain ganglia of the broncho-pulmonary system, of the gastro intestinal tract,

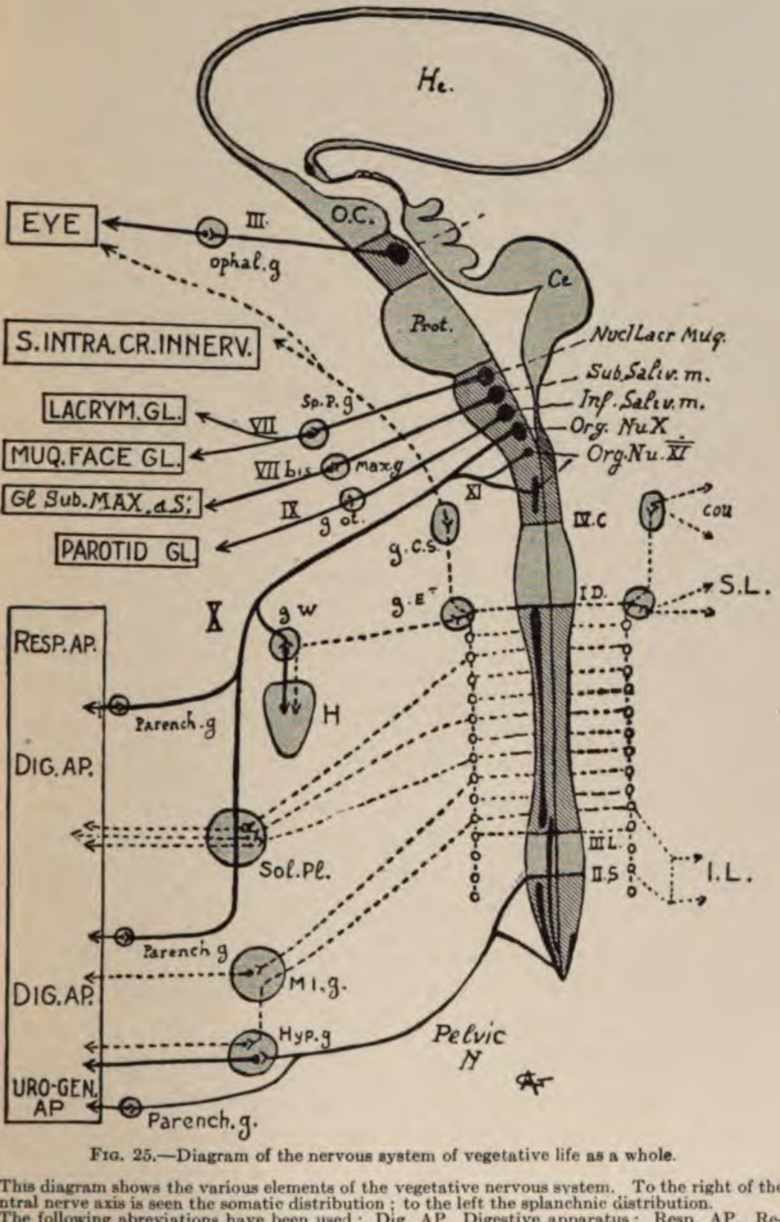


FIG. 25.—Diagram of the nervous system of vegetative life as a whole.

This diagram shows the various elements of the vegetative nervous system. To the right of the central nerve axis is seen the somatic distribution; to the left the splanchnic distribution.

The following abreviations have been used: Dig. AP. Digestive apparatus; Resp. AP. Respiratory apparatus; Uro-Gen. AP.Urogenital apparatus; Ce Cerebellum H. Heart; O. l. Optic layer; G. sp. s. Sup. Cervical Ganglion; Hyp. G. Hypogastric ganglion; Max. G. Maxillary ganglion and ganglion of Langley; i. M. G. Inf. Mesenteric ganglion; Parench. G. Parenchymatous ganglion; Sp. P. G. spheno palatin ganglion; G. W. ganglion of Wrisberg; S. L. and I. L. Superior and inferior limb; Sol. Pl. Solar plexus.

.... Indicates the lumbar thoracic or true sympathetic.

– – – – – – – – – – – – Indicates the cranial pelvic or parasympathetic system.

of the genito urinary apparatus, which are under the dependence of the vagus and the pelvic plexus.[5]

In the second group we have the autonomous systems of the heart, gastro intestinal tract, and urinary tract, which are constituted of parenchymatous ganglia and autonomous cells not grouped in ganglia.

Among the parenchymatous ganglia and the intra visceral nerve cells there exist (outside of the sensory cells):

1.—Ganglionic or cellular groups which depend on the greater systems and which practically cannot get along without them; these are the long arc motor systems.

2.—Ganglionic and cellular groups relatively independent of the vegetative system of the nerve axis, which can be influenced by them, but can function independently from them. These are the short reflex arcs which keep up life in an organic segment when separated from all central connection, as long as chemical media is adequate.

To complete the study of the components of the vegetative system, we must also describe the glandular element, the glands of internal secretion, which, by their harmonies help to regulate the vegetative system. This question will be stated ultimately.

IV. ANATOMICAL AND PHYSIOLOGICAL DESCRIPTION OF THE VARIOUS SYSTEMS.

We have just seen that among the various elements of the vegetative nervous system we must distinguish:

1.—Higher centres;

2.—Spinal centres;

3.—A peripheral system composed of fibres and ganglia.

Finally, we have also seen that in the last-named group there were:

---

[5] These two nerve elements, the vagus and the pelvic plexus, both have their ganglia as near as possible to the viscera, in this way differing from the sympathetic.

(*a*) A certain number of elements, physiologically dependent on the spinal centres;

(*b*) A certain number of elements, partially independent of the spinal centres, real autonomous centres. We must now study the grouping of the various components into systems. Here anatomy is no longer of much help and we must depend mostly upon physiology. For this reason we are going to study jointly from a morphological and physiological point of view each of the vegetative nerve tracts. In studying these, we shall proceed from top to bottom of the nerve axis, that is, from the cerebral peduncle to the end of the spinal column.

I. VEGETATIVE SYSTEM ARISING FROM THE CEREBRAL PORTION.

We remember that at the level of the cerebral peduncle, we find a series of vegetative nuclei which are divided in the following manner:

In the cerebral peduncle a nucleus (pupillary) annexed to the III cranial nerve.

In the bulb, 6 nuclei, the first (lacrymal mucous-facial) annexed to the facial, the second (superior salivary) annexed to the intermediate, the third (inferior salivary) annexed to the glosso pharyngeal, the fourth (vagus) and the fifth (spinal) annexed to the vagus, the sixth (vaso motor) annexed to the hypoglossal.

A. PHYSIOLOGY OF THE VEGETATIVE SYSTEM OF THE III CRANIAL.

The vegetative fibres arising from the pupillary nucleus travel with the fibres of the III cranial up the ophthalmic ganglion; they then abandon the oculo-motor and enter the ganglion where they terminate and communicate with the ganglionic cells. These ganglionic cells give birth to fibres which travel by way of the short ciliary nerves, to end in the eyeball.

1.—The sphincter muscle of the iris (closure, myoses).

2.—The ciliary muscle (accommodation, by action upon the crystaline lens)

Such is the vegetative motor arc annexed to the oculomotor. The axial centre is the pupillary nucleus, the central ganglionic fibres, the vegetative fibres contained in the III, then the fibres of the short root of the ciliary ganglion; the ganglionic centre is in the ciliary or ophthalmic ganglion from which arise the ganglion organic fibres, which, by way of the short ciliary nerves, reach the vegetative fibres of the eye.

The sensory arc is represented here by the sensory tract of the optic nerve, but I will not go into detail of the complete reflex arc; diagram 26 explains this sufficiently; it also explains the phenomenon of Wernicke, that is, absence of the pupillary reflex when the rays of light strike the blind half of a hemianopsic eye, phenomenon which is symptomatic of lesions of the optic tract and one of the differential points between these and central lesions.

B. PHYSIOLOGY OF THE VEGETATIVE SYSTEM ANNEXED TO THE VII CRANIAL NERVES.[6]

These vegetative fibres, arising from the lacrymal-mucous-facial nucleus follow the course of the VII nerve as far as the geniculated ganglion; then, leaving this nerve, follow one of its branches, the great superficial petrosal nerve, then with the vidian nerve, reach the spheno-palatin ganglion, where they end and communicate with ganglionic cells from which fibres arise which follow the various branches of the superior maxillary branches of the trifacial and controls the secretion of:

---

[6] In order to better understand this paragraph and the following see Figs. 25 and 29

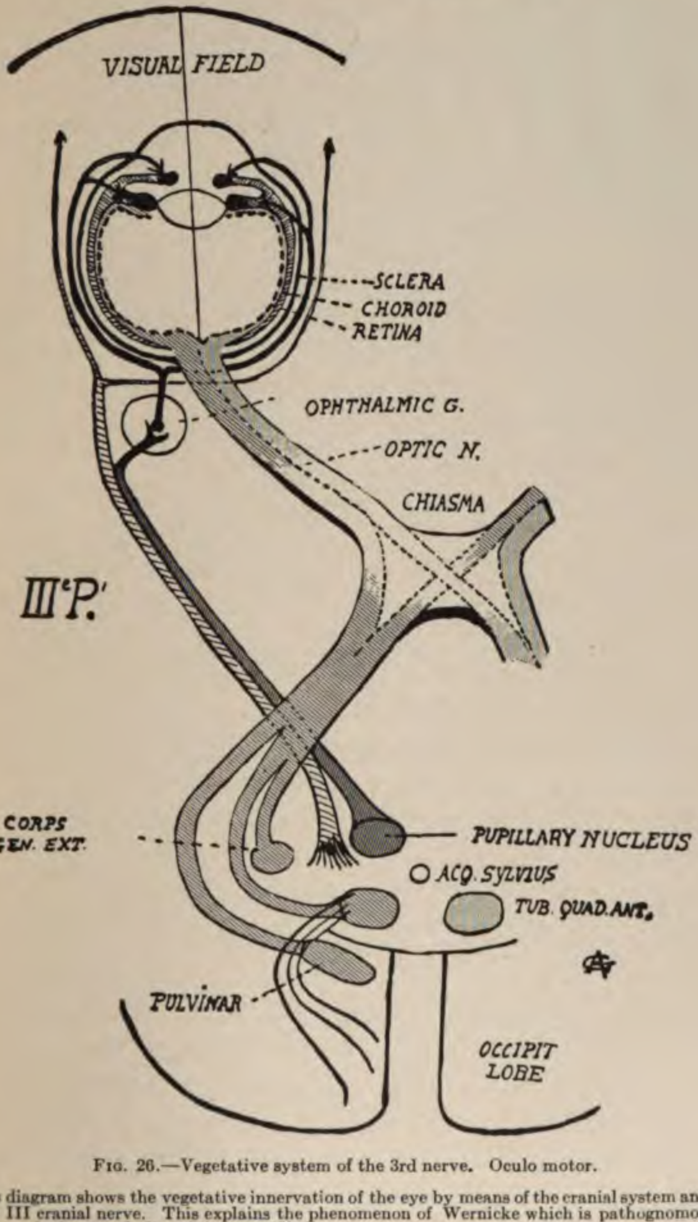


Fig. 26.—Vegetative system of the 3rd nerve. Oculo motor.

This diagram shows the vegetative innervation of the eye by means of the cranial system annexed to the III cranial nerve. This explains the phenomenon of Wernicke which is pathognomonic of hemianopsia due to a lesion of the outer fibres.

A ray of light striking the blind half of the eye will not give rise to a motor reflex of the pupil, in this differing from a cortical hemianopsia.

1.—Lacrymal glands.

2.—Mucous glands of the nose and the pharyngeal region in the neighborhood of the nose.

The motor vegetative arc is, therefore, constituted by a central nucleus, the lacrymal mucous-facial nucleus, from which a central ganglionic neuron arises (which follows successively the course of the facial, greater superficial petrosal, vidian); a ganglionic nucleus (the spheno-palatin nucleus), from there arises a ganglion-organic neuron, which by a series of branches of the superior maxillary reaches its various endings.

The afferent sensory arc is represented by the sensory part of the trigeminal.

C. PHYSIOLOGY OF THE VEGETATIVE SYSTEM ANNEXED TO THE VII.

The central nucleus is the superior salivary from which arise the vegetative fibres which, by the intermediary nerve of Wrisberg, the corda tympani, the lingual of the trigeminal, reach to the sub-maxillary or maxillary ganglion which they penetrate. Some fibres end in the ganglion and communicate with the ganglionic fibres, others simply go through it and reach a microscopic ganglion, the ganglion of Langley where they end and anastomose with the ganglionic cells. From the ganglionic cells of the ganglion arise ganglion-organic fibres which reach the sublingual gland; from the cells of the ganglon of Langley also arise ganglion-organic fibres, which reach the submaxillary gland.[7] These ganglion-organic fibres control the secretions of the sub-maxillary and sub-lingual glands.

The motor arc is, therefore, as follows: central ganglionic neuron from the superior salivary nucleus to the maxillary and Langley ganglia, passing by way of the intermediary nerve of Wrisberg, the corda tympani, the lingual, the two roots of the maxillary ganglion; ganglion-organic neuron —from the cells of the two ganglia to the glandular tissue.

---

[7] This is a physiological fact.

The sensory arc is represented by the inferior maxillary, the trigeminal, the sensory roots of the intermediary nerve of Wrisberg.

D. PHYSIOLOGY OF THE VEGETATIVE SYSTEM ANNEXED TO THE IX CRANIAL.

The vegetative fibres arising from the inferior salivary nucleus travel with the fibres of the IX in that part of the nerve between the central axis and the ganglion of Andersch.

Here the fibres follow one of the branches of the IX, the nerve of Jacobson and finally reach the optic ganglion, or ganglion of Arnold where they end and anastomose with the ganglionic cells. From these cells arise new neurons which follow the auriculo-temporal nerve and reach the parotid gland. These fibres control the secretions of these glands.

The motor arc is therefore as follows: central ganglionic neuron—from the inferior salivary nucleus to the optic ganglion passing by the IX nerve, Jacobson's nerve, the deep petrosal nerve, ganglion-organic neuron—from the optic ganglion to the gland, passing by way of the auriculo-temporal.

The sensory arc is represented by the sensory part of the trigeminal and by the sensory tracts of the glosso pharyngeal and the intermediary nerve.

E. PHYSIOLOGY OF THE VEGETATIVE SYSTEM ANNEXED TO THE X CRANIAL (VEGETATIVE VAGUS)

If we leave out a small area which is related to motor life of the voluntary system (pharynx, soft palate and larynx), we must consider the vagus as the chief nerve of the vegetative system. This nerve controls the excito-motor stimulation for: 1.—The gastro intestinal tract from the œsophagus to the beginning of the large intestines. 2.—All the vegetative fibres of the respiratory system. 3.—The excitory secretory stimulation of the glands annexed to the gastro intestinal tract. 4.—That of the glands annexed to the digestive tube. 5.—That of the glands of the respiratory tract. 6.—Inhibits the cardiac contractions.

The importance of the vagus in the vegetative life is, therefore, considerable. The vegetative fibres of this nerve come:

1.—From the dorsal nucleus of the vagus;

2.—From the bulbar and medullary nuclei of the IXth. These fibres constitute the greater part of the vegetative fibres. We must add, however, that certain fibres, belonging really to the thoracic-lumbar portion of the vegetative system, join the vagus by means of the anastomosis of this nerve with the ganglia of the true sympathetic system.

From the central vegetative nuclei arise particularly long central ganglionic fibres, which reach the ganglia in the neighborhood of the organs, for instance, the ganglionic plexus of Wrisberg or numerous parenchymatous ganglia of the gastro intestinal tract. There these fibres end and communicate with the ganglionic cells from which the ganglion-splanchnic fibres arise, which reach the vegetative tissues. These fibres are short.

The motor arc is, therefore, as follows:—Long central ganglionic fibres, short ganglion—organic fibres. The sensory arc consists of the sensory fibers of the vagus.

F. PHYSIOLOGY OF THE VEGETATIVE SYSTEM ANNEXED TO THE XII CRANIAL.

This is made up of vaso-motor fibres which are distributed to the blood vessels of the tongue and really belong from a physiological point of view to the thoracic lumbar system.

II. VEGETATIVE SYSTEM ARISING FROM THE CORD.[8]

From the point of view of vegetative centres, we must divide the cord into three regions which correspond to three sets of vegetative fibres.

1.—The part superior to the cervical cord (above the IV cervical segment).

2.—The portion of the cord found between the two following limits:

(*a*) Superior limit, I or II dorsal segment.

(*b*) Inferior limit, the III or IV lumbar segment.

This region is called the thoracic-lumbar region of the vegetative nervous system or true sympathetic system.

3.—The portion of the cord below the V lumbar segment; this is the sacral portion or pelvic segment of the vegetative system.

We shall now study each of these segments individually.

A. MEDULLARY CERVICAL VEGETATIVE PORTION.

The vegetative fibres which arise from this area, go up towards the head by means of the medullary root of the spinal nerve and with this nerve reach the vagus.[9]

B. THORACIC-LUMBAR MEDULLARY PORTION.

From the vegetative column, formed by the superposition of the intermediar lateral nuclei of the anterior horn of the medullary segments, arise vegetative fibres which follow, first, the anterior roots, then the white rami communicant, and finally reach the sympathetic ganglia of the lateral chain. We have seen how, in the simplest case, these fibres end and communicate with one or more ganglionic cells, which cells give rise to ganglion-organic axions made up of gray fibres. Some of these axions go to the periphery (ganglion-somatic fibres) joining by means of the gray rami communicantes the spinal nerve, while others reach the viscera by means of the splanchnic vegetative nerves ganglion-splanchnic fibres.

---

[8] See Figs. 25 and 27.

[9] We have already studied these with the vagus.

We have also studied the various ways the central ganglionic fibres end, the origin and ending of the ganglion-splanchnic fibres; finally, we have studied the commissural fibres. It is, therefore, easy for us to conclude that *the thoracic-lumbar part of the vegetative system, the real sympathetic is made up of:*

1.—A central motor, medullary part, the vegetative intermediolateral column, included between the I, II dorsal segment and the III, IV lumbar.

2.—Central ganglionic fibres which by means of the white rami communicantes of the nerves corresponding to these segments, reach a ganglion belonging to one of the three rows of ganglia (vertebral row, visceral row, parenchymatous row).

3.—Ganglion-organic fibres, somatic or visceral, which arise:

(*a*) From the ganglia of the lateral chain for the somatic distribution;

(*b*) From any one of the three rows for the splanchnic distribution.

The diagrams attached to this book explain this far better than any long description:

(*a*) The general disposition of the thoracic-lumbar or sympathetic part of the vegetative system;

(*b*) The topographical distribution of the nerves of this system;

(*c*) The relationship of these endings with their medullary origin.

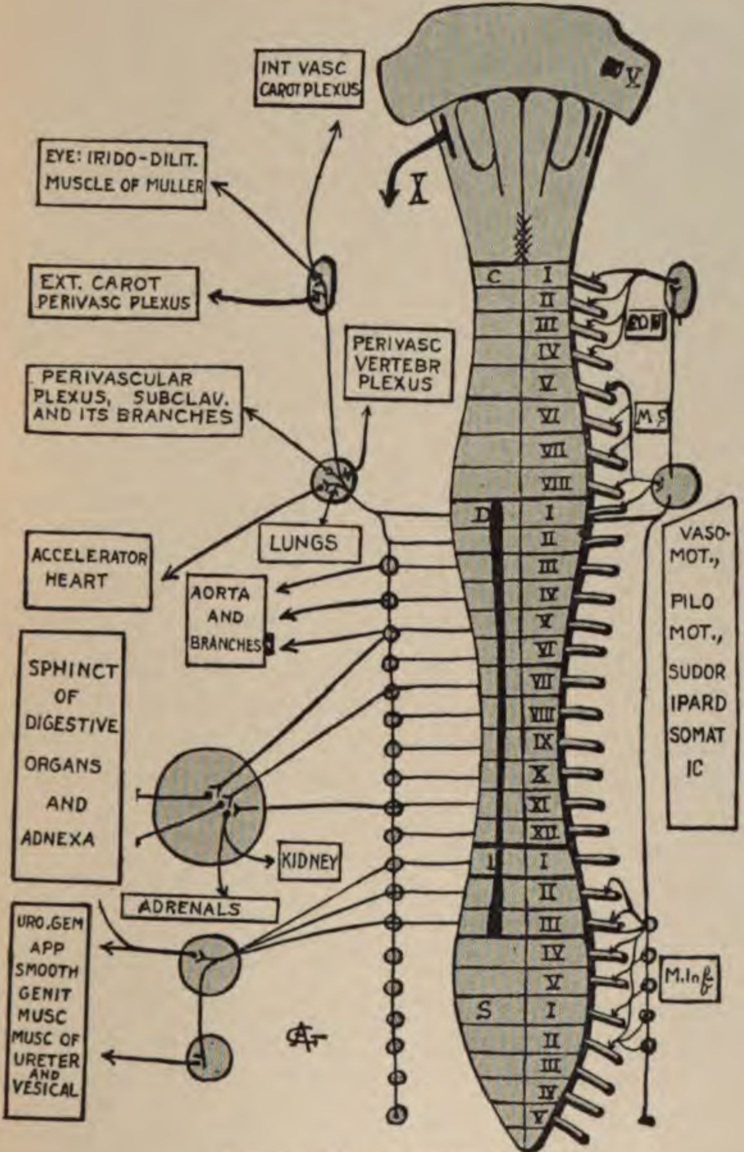

INT VASC CAROT PLEXUS
V
EYE: IRIDO-DILIT. MUSCLE OF MULLER
X
EXT. CAROT PERIVASC PLEXUS
C
I
II
III
IV
V
VI
VII
VIII
PERIVASC VERTEBR PLEXUS
PERIVASCULAR PLEXUS, SUBCLAV. AND ITS BRANCHES
M S
LUNGS
D
ACCELERATOR HEART
AORTA AND BRANCHES
IX
X
XI
XII
VASO-MOT., PILO MOT., SUDORIPARD SOMATIC
SPHINCT OF DIGESTIVE ORGANS AND ADNEXA
KIDNEY
ADRENALS
L
URO.GEM APP SMOOTH GENIT MUSC MUSC OF URETER AND VESICAL
M.Inf
S

Fig. 27.—Thoracico-lumbar portion.

This diagram shows the general disposition of the thoracic lumbar (or true sympathetic) portion of the vegetative nervous system. The intra medullary column, formed by the superposition of the vegetative axis central nuclei, is drawn in black between D 1 and L 3 on the left half of the spinal axis. On the same side (in this diagram) arise the connecting central ganglionic fibers going to the lateral chain. Some of the fibers go through the lateral chain to reach the solar plexus or inferior mesenteric plexus (and its dependency the hypogastric plexus). The majority of the fibers connect with the ganglionic cells of the lateral chain from which arise the ganglionic organic fibers. As regards to these fibers the somatic distribution is shown on the right, the splanchnic distribution on the left.

PHYSIOLOGY OF THE THORACIC-LUMBAR, OR TRUE SYMPATHETIC PART OF THE SYSTEM.

The functions of this part are more general than that of the rest of the vegetative system. The sympathetic controls: 1.—The smooth muscles of the blood vessels; 2.—The smooth muscles of the skin; 3.—The secretion of the sudorific glands; 4.—The smooth muscles sphincters of the gastro-intestinal tract from the stomach to the rectum; 5.—The muscles of the ureter, vesical trigone and sphincter of the urethra; 6.—The smooth muscles of the genital organs in the two sexes, and the retractor penis; 7.—In the occular region the irido-dilator and the muscle of *Mueller*.

Furthermore, we must add to the functions of the true sympathetic: acceleration of the heart, shortening of the cardiac systole. From the point of view of general metabolism there are many changes, the most simple being glycosuria and one of the most complicated the regulation of body heat; finally, we must not forget the inhibitory phenomena of the contraction of muscle, which counterbalances the excito-motor innervation of the cranio pelvic system of the vagus and pelvic plexus.

This enumeration of the various functions of the sympathetic would be of very little use if we did not go more fully into details.

As regards the vaso-motor system, there is nothing very particular to say; but as regards the gastro intestinal tract, leaving aside temporarily the inhibition to contraction, there are certain interesting facts in so far as the innervation of the smooth muscle sphincters are concerned.

We know that the true sympathetic gives to a certain part of the gastro-intestinal tract an innervation antagonistic to that of the vagus, but it is perfectly evident that the nervous control of the true sympathetic is much more restricted than that exerted by the vagus and the pelvic plexus.

The English have shown that the true sympathetic controls all the sphincters of the large intestines, all those of the small intestines and some of those of the stomach.[10] In these regions this system gives off excito-motor impulses to the sphincters and inhibitory impulses to the rest of the tube.

As regards the part played by the true sympathetic in the upper portion of the gastro intestinal tract (cardiac, esophageal) this has not as yet been elucidated. We can, however, infer until further proof that: *the superior limit of control of the true sympathetic passes by the stomach.*

In spite of its importance this question has not yet been settled. Cannon has thrown some light on the subject. He showed that the stomach is made upof two distinct portions; the cardiac portion is a passive cavity for the reception of food, and the pyloric portion which is the active portion of the stomach, the one that generates the peristaltic movements which cause the food to be propelled into the intestines.

Cannon furthermore has shown that the limit of the two portions of the stomach is at the level of the gastric cardiac notch (since the movements of the stomach begin exactly at that point).

Finally, Cannon has demontrated, and so have other physiologists, that the excito-motor, as well as the inhibitory enervation of the cardiac portion of the stomach and its sphincter is controlled by the vagus and the vagus alone; while the pyloric portion is enervated both by the true sympathetic and the vagus. The exact anatomical limit of the true sympathetic control of the stomach corresponds to the cardiac notch.

---

[10] In regards to the pylorus there is a double enervation, but the part played by the sympathetic stimulation cannot be denied, if we only consider the direct physiological effect and keep in mind the local mechanism.

As regards the control of the sphincters of the bladder and of the urethra it is easy to understand, if we remember that the bladder and the urethra come from the vesico urethral portion of the urogenital sinus, itself part of the cloaca, which is made of a portion of the terminal intestines. We also know that the cloaca, in the process of evolution, divides itself into an intestinal part (coprodeum) and a urinary part (urodeum). The bladder and urethra on one side, the colon and anus on the other are, therefore, parallel derivatives of the same origin and it is only natural that the enervation of these two systems should be the same.

As far as the large intestine is concerned, we know that from the excito-motor point of view it is enervated by the pelvic plexus and the excito motor enervation of the smooth muscle sphincter is controlled by the true sympathetic; it is, therefore, natural that the sphincters of the bladder and urethra should be stimulated by the true sympathetic and the rest of the musculature by the pelvic plexus.

As regards the urethra and the genital organs, the sympathetic enervation has an entirely different cause which is easily understood if we know that this system controls the smooth muscle fibres of the system derived from the canals of Wolff and Muller.

There are two other important points to take into consideration, namely, the effect of the stimulation of the sympathetic on metabolism and the phenomenon of inhibition on the active contraction of certain smooth muscles due to stimulation by the vagus or pelvic plexus.

As far as stimulation of the sympathetic on metabolism is concerned, it is not necessary to invoke the direct action of this system on cellular elements.

We know that the true sympathetic acts upon the vasomotor system and also that it plays a part on the production and liberation of hormones. Two different hypotheses can, therefore, be brought forward as regards the action of the true sympathetic on metabolism. It is possible that circulatory changes occur within organs which cause changes in the glandular functions of the cells. This probably explains certain of the phenomena, but not all. We must, therefore, in order to explain these refer to the action of the hormones, by their direct and indirect action on the glands of internal secretion.

As regards the phenomenon of inhibition produced by stimulation of sympathetic fibres, here again circulatory changes play a part and we must not forget, that according to the latest findings, the mechanism of inhibition does not necessitate inhibitory fibres. These phenomena can be entirely due to changes in the contact of the nerve and the tissue and which may occur in any stimulating fibre, providing the articular membrane of the neuron is in a proper physicochemical condition.

If we, therefore, look at the enervation of the true sympathetic as a whole we see that it is primarily vascular (smooth muscles of the blood vessels) and dermic (smooth muscles of the skin glands). In a rather ingenious hypothesis, which, however, must be studied and confirmed, Gaskell considers the digestive sphincters as a supplementary covering of the gastro intestinal tract, which has nearly disappeared and which left only remains in the shape of the sphincters. This tunic, according to Gaskell, is also dermal in origin,[11] and this is why he calls the true sympathetic the vaso-dermal system, believing, as does

---

[11] Certain recent embryological researches seem to confirm Gaskell's theory.

Keith and others, that the segmentary canals from which are derived the canals of Wolff and Muller are of epiblastic origin and not mesoblastic, as generally admitted.

There is, however, in all this a certain amount of imagination and however attractive the theories of Gaskell may be, we cannot, nevertheless, make use of them as a basis for a series of deductions. We must, therefore, stop here and conclude:

(*a*) That the true sympathetic appears to have from a morphological as well as from a physiological point of view much more general functions than the cranio pelvic or parasympathetic system;

(*b*) That sympathetic enervation is found in all the organic processes of the body, particularly bodily heat and cellular metabolism and, as says Max Verworn: "There is no living matter which is not made up of cells and there is no function of living matter which does not originate in an element vital phenomenon of the cell." We can say that the true sympathetic acts primarily on cells in general; its place in vegetative life is most important. Inversely, all changes in the sympathetic show themselves by important modifications in cellular life, and in persistent changes in the true sympathetic, organic metabolism will be very much affected.

C. MEDULLARY SACRO-COCCYGEAL VEGETATIVE PORTION.[12]

From the vegetative nuclei of the sacro-coccygeal portion of the cord arise vegetative fibres which, united as the pelvic plexus, reach the ganglionic plexuses of the pelvis, made up of the colo rectal plexus which sends motor impulses to the large intestines (except the sphincters) and the vesical plexus which sends motor impulses of the detrusor.

---

[12] See Figs. 25, 27 and 29.

Let us add that the pelvic plexus helps in the enervation of the blood vessels of the anal mucous membrane and the external genital organs.

III. THE LOCAL VISCERAL SYSTEMS.

The vegetative systems which we have just gone over, are not the only representatives of the nervous system of vegetative life.

Next to these systems there exists local visceral systems mostly independent of the systems we have just studied. The existence of these systems is proved by the phenomena observed when tissues are separated from the organism and placed in a proper medium. It is thus that we detect the presence of local cardiac, digestive, genital and other systems that we know, or only suspect the existence.

The knowledge of these local autonomous systems must make us modify our conceptions on the physiopathological part played by the central visceral vegetative nervous systems. It appears that as far as the determination of movement in smooth muscle is concerned, their part, although necessary, is not indispensable. *The only indispensable nervous systems are the local nervous systems.* The local nervous systems are systems of cells and organs and the central organic vegetative nervous systems are systems of organisms.

From a physiological point of view the local systems are not well known; their systematization in particular, is very uncertain; the best known are those of the heart (ganglionic knot, auricular sinus, bundle of His, ganglionic system of this bundle and ventriculo arterial endings).

In the case of the heart there exists therefore:

1.—An indispensable system, the local cardiac system.

2.—Two necessary nervous systems, the central splanchnic systems of the vagus and the sympathetic.

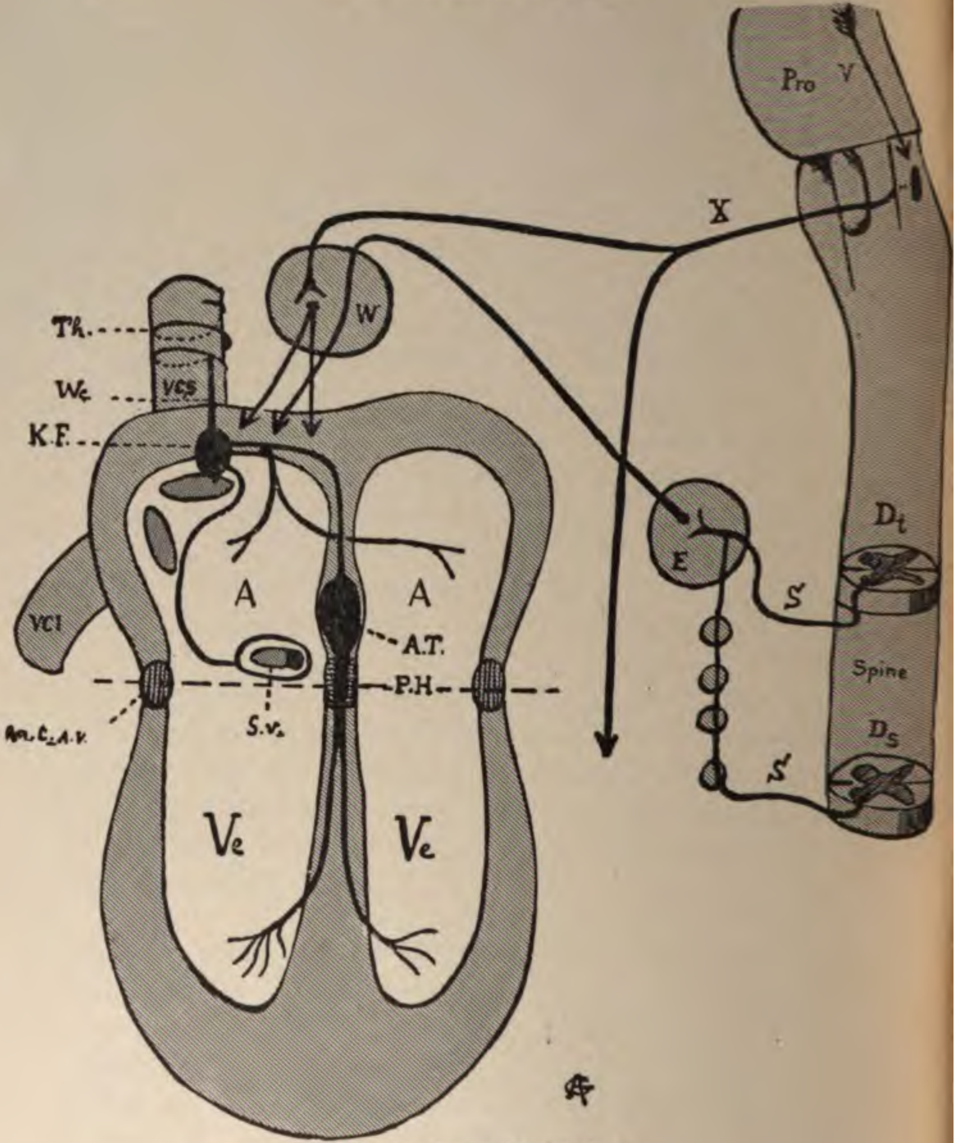


Fig. 28.—Innervation of the heart.

This diagram shows to the right the nerve axis, to the left the heart.

In the axis Pro. means Pons Varoli: D1 and D5 indicate medullary segments located at the extremity of the medullary cardiac zone; S. Indicates the thoracic central ganglionic fibres and the Stellar ganglion.

On the side of the heart: W indicates the ganglionic plexus of Wrisberg; A indicates the auricles, Ve the ventricles, Au t. A. V. the auriculo ventricular bundle; V. C. S. and V. C. I. the superior and inferior vena cava; S. V. sinus venosus.

The nerve connection is therefore as follows: 2 axis centres, one in the bulb, the other in the spinal column and under the control of the higher centres. (V). They are connected with the heart, by means of the vegetative fibres of the vagus for the bulb (interrupted in the plexus of Wrisberg) and by means of the true sympathetic for the cord (interrupted in the Stellar ganglion). The autonomic system of the heart is made up of the superior bundle of THOREL (Th.), the auricular venous fibres or Wenckenbach (We), the nodes of Keith and Flack (K. F.) and their auricular connections, the nodes of Aschoff-Tawara (A. T.) continued by the bundle of Paladino-His (P. H.) down to the ventricles.

The vagus inhibits the cardiac contraction by means of a central ganglionic neuron which goes from the bulb to the ganglia of Wrisberg and a ganglion-splanchnic neuron which goes from the ganglion of Wrisberg to the heart. The sympathetic accelerates the heart by means of a central-ganglionic cell which goes from the superior portion of the dorsal cord to the star ganglion and from there a ganglion-neuron which reaches the heart.

IV. THE VARIOUS NERVOUS SYSTEMS OF AUTONOMIC LIFE AS A WHOLE.[13]

From a morphological and physiological point of view, going from the simple to the complex, we see that the vegetative nervous system is composed as follows:—

1.—Local systems.

2.—Central splanchnic systems connected with two neurons, one a central ganglionic neuron, the other a ganglion-organic neuron.

3.—A co-ordinating system, organic co-ordination, animal co-ordination, organo-psychic co-ordination and inversely. These systems are represented by association medullary tracts or medullo cephalic tracts. Finally, in the higher centres, the encephalo-encephalic association tracts.

How shall we group these various elements? All evidence points to the fact that the local systems belong to the organs which they control; there is a local system for the heart, for the stomach, for the intestines. It becomes however, more complicated when we reach the central splanchnic systems. Here one fact stands out prominently and that is the very general character of the distribution and control of the true sympathetic which has been called vaso-dorsal by Gaskell. Another important fact is: The extension of the vegetative enervation assured by the vagus, which controls the gastro intestinal tract and its embryological derivatives, such as the respiratory tract and the digestive glands. This importance of the vagus is further emphasized if we realize that the pelvic plexus completes the inferior portion of the gastro intestinal tract. We must, therefore, group as one system these two anatomical entities, the vagus and the pelvic plexus. We must also remember that from the bulb arise vegetative fibres which go to the glands located at the upper portion of the openings of the respiratory and digestive tracts; these are annexed to the VII and IX cranial (system of the lacrymo mucus, facial, inferior and superior salivary nuclei). We can physiologically separate the central splanchnic vegetative system of the vagus, from the homologous systems of the pelvic plexus and the other vegetative bulbar nuclei (exception being made of the nucleus annexed to the XIIth).

---

[13] See Figs. 25, 27 and 29.

This should go under the name of nervous vegetative digestive system, including under the name of digestive the various evolutions of the gastro intestinal tract and its physiological annexes.

This leaves us only one vegetative central organic system; the vegetative system annexed to the ocular muscle. We have seen that physiologically this system is more or less opposed to the ocular enervation coming from the true sympathetic. We can, therefore, classify the system of the III in the same group as the nervous digestive systems and oppose to the true sympathetic a second system which I have called the parasympathetic.

From now on I will use these two terms, sympathetic and parasympathetic, to designate the two antagonistic parts of the vegetative systems. Finally, to complete our studies, we must investigate the grouping and the morpho-

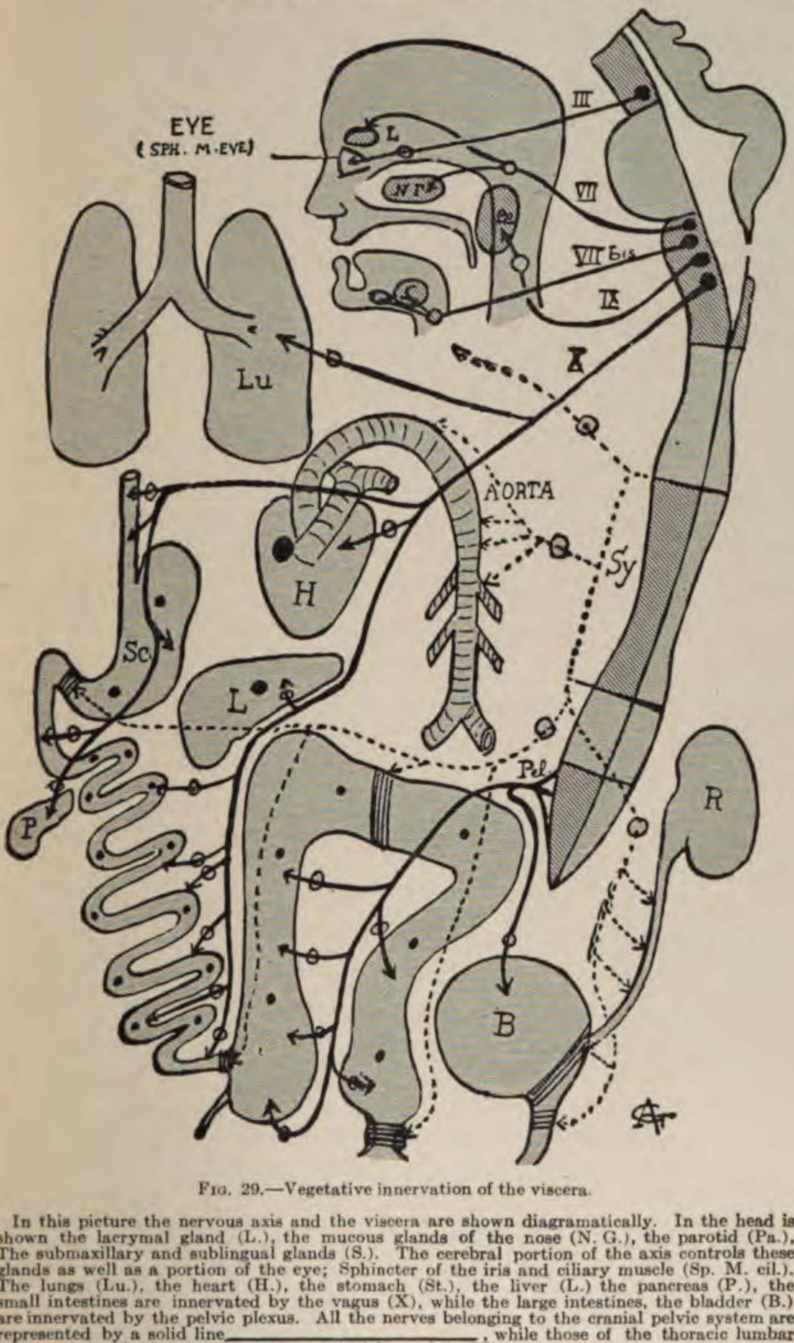


Fig. 29.—Vegetative innervation of the viscera.

In this picture the nervous axis and the viscera are shown diagramatically. In the head is shown the lacrymal gland (L.), the mucous glands of the nose (N. G.), the parotid (Pa.), The submaxillary and sublingual glands (S.). The cerebral portion of the axis controls these glands as well as a portion of the eye; Sphincter of the iris and ciliary muscle (Sp. M. cil.). The lungs (Lu.), the heart (H.), the stomach (St.), the liver (L.) the pancreas (P.), the small intestines are innervated by the vagus (X), while the large intestines, the bladder (B.) are innervated by the pelvic plexus. All the nerves belonging to the cranial pelvic system are represented by a solid line______________________, while those of the thoracic lumbar or true sympathetic system are represented by a dotted line............................... The true sympathetic innervation is drawn very sketchily and for further details see fig. 27. This diagram however shows the uro-digestive sphincter innervation of this system. The various dots, scattered in the viscera indicate autonomous systems.

logical methods of progression of the vegetative systems of co-ordination, the vegetative association tracts. At the beginning I have explained the morphology of these systems and I will not repeat again. I will content myself to indicate that in a general way the pathways of vegetative life do not differ essentially from tracts found in the nervous axis and in the brain.

V. PHYSIOPHARMACOLOGICAL OPPOSITION OF THE TWO GREAT VEGETATIVE SYSTEMS.

We have just seen that by their physiological opposition we can divide the vegetative system into two groups; the sympathetic and parasympathetic. This opposition becomes still more evident if we study these two systems from a pharmacological point of view.

I. ELECTIVE ACTION OF CERTAIN SUBSTANCES ON THE VEGETATIVE SYSTEMS.

When we study substances which we consider as products of internal secretions,[14] we are struck by the fact that they have an elective action upon the systems of vegetative life, for their introduction into the organism stimulates, or depresses, the action of these systems. This is a fact of prime importance.

It is not necessary at present to go into details of the pharmocodynamic action of the organo elective substances. We will come back to this presently. At present we shall study certain more general facts on the action of the various substances on the vegetative nervous systems.

II. PHARMACOLOGICAL ANTAGONISM OF THE NERVOUS SYSTEMS OF VEGETATIVE LIFE.

The substances having an elective action on the nervous systems of vegetative life can be divided into two groups:

---

[14] The extracts of organs are not necessarily identical to hormones.

1.—Substances acting on all the components of the vegetative system.

2.—Substances acting only on certain components.

The first group does not deserve much study; the second, however, is worth while explaining.

Certain substances act only upon certain vegetative nervous systems and what is remarkable is that this electivity is copied practically exactly on the great morphological and physiological division of the systems into:

Cranio pelvic system or parasympathetic;

Dorsal lumbar system or sympathetic.

That is, there are, among the substances having a partial action, certain ones which manifest themselves by their action upon the parasympathetic and others upon the sympathetic and this action will be equivalent, all things being equal, to stimulation or paralysis of the system as a whole. Finally, there are substances having a partial action, products which do not act upon the total system, but only one of its parts still however, respecting the law of pharmacological electivity.

III. OUR IDEA OF PHARMACOLOGICAL TONUS.

If one of the systems of vegetative life is stimulated, this stimulation will manifest itself in the parts enervated by this system. There will be hypertonia of this system. If this system is in a state of paralysis or inhibition, there will be hypotonia of this system. From this, two major ideas are brought to the front: hypertonia and hypotonia of the vegetative nervous systems.

So far there is nothing very complicated to this: it is easy to understand that in the physiological, as well as the pathological state, substances, be they endogenous or exogenous, can produce in healthy or sick subjects, phenomena equivalent to stimulation of a whole or part of one of the systems. If we study a patient, keeping these facts in mind, we are struck by the discovery of certain findings which seem to disprove the preceding conclusions.

Let us take a practical example. Should we depress the parasympathetic system, what do we observe? In all parts of the organism where the parasympathetic system is represented there will be hypotonia, that is, a retardation of the functions in progress, but on the other hand, in those parts of the body which receive both sympathetic and parasympathetic enervation, phenomena will appear which will be equivalent to stimulation of the sympathetic in those parts. This is what has been termed the paradox of tonus, due to the fact that as the parasympathetic tonus decreases, the sympathetic tonus, which was balanced by it, becomes predominant and appears as a hypertonia of the sympathetic.

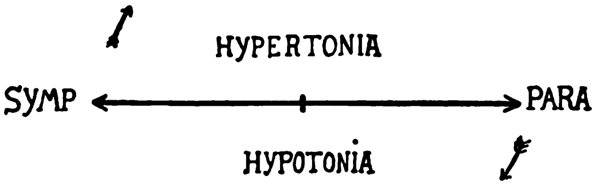


FIG. 30.—Diagrammatic demonstration of the paradox of tonus.

There is, therefore, a balance of tonus of the two systems whenever they are present together. If for one cause or another, by action on one or the other, the equilibrium is disturbed, as one is depressed, the other automatically becomes more prominent.

The following mechanical example illustrates this phenomenon and its significance. Suppose we take a weight A in equilibrium between two equal forces. If we wish to displace the weight towards C we can accomplish this in two different ways. By increasing the traction towards C, or in decreasing the traction towards B.

Applying this notion to the pupillary reaction, we know that:

(*a*) The parasympathetic innervates the sphincter of the iris and that stimulation of it will cause myosis;

(*b*) The sympathetic innervates the irido-dilator and its stimulation causes mydriasis. If, therefore, we pharmacologically wish to produce mydriasis, we act in the following manner:

(*a*) By paralyzing the parasympathetic (atropin).

(*b*) By stimulating the sympathetic (adrenalin).

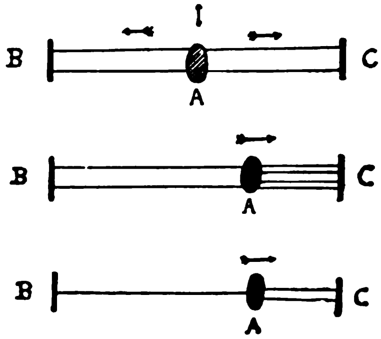


FIG. 31.—Showing diagrammatically the mechanism of disturbance of equilibrium.

We cannot insist too much on these facts, for their importance is tremendous. This principle is the basis for the greater portion of our knowledge of the physiology and pathology of the neuro glandular systems of vegetative life. It is through these principles that we are able to understand the action of reciprocity of the nervous and endocrine elements.

IV. TOTAL TONUS. PARTIAL TONUS.

We have seen that there exists, under the influence of certain substances, a state of tonus of all or part of the nervous systems of vegetative life. This tonus may manifest itself as a stimulation or depression. Finally, in territories having both systems antagonistic to each other, hypotonia of one system will manifest itself as a hypertonia of the other.

This being understood, it will be easy to divide the tonus of the nervous systems of vegetative life. The classification is as follows:—

1.—If the two systems are acted upon at the same time there will be:

$$\left.\begin{array}{l}\text{hyper}\\ \text{hypo}\end{array}\right\}\text{general tonus}\qquad\text{or}\left\{\begin{array}{l}\text{hyper}\\ \text{hypo}\end{array}\right.\text{neurotonia}$$

2.—If one of the systems alone is affected there will be:

$$\left.\begin{array}{l}\text{hyper}\\ \text{hypo}\end{array}\right\}\text{Tonus of}\left\{\begin{array}{l}\text{sympathetic or sympathicotonia}\\ \text{parasympathetic or parasympathicotonia.}\end{array}\right.$$

In the following chapter will be given a clinical description of the sympathicotonia and parasympathicotonia syndrome.

V. THE SUBSTANCES ACTING UPON THE NERVOUS SYSTEMS OF THE VEGETATIVE LIFE.

These substances are: 1.—Exogenous, or 2.—Endogenous.

The exogenous products are: drugs or poisons. Their number is only limited because of the paucity of our knowledge.

The endogenous products belong to two groups:

1.—Products resulting from the secretions of the endocrine glands, the hormones.

2.—Products resulting from the normal or pathological function of various organs of the body.

As far as the hormones are concerned, there is considerable to be said, but our knowledge of these products is increasing daily, so that conclusions which are reached to-day may have to be modified to-morrow. If we study the pharmacological action of the endocrines, we are struck by the fact that while they all act more or less on the nervous systems of the vegetative life, certain ones have an elective action on one or part of one system. Suprarenalin, the product of the medullary portion of the suprarenal capsule is a good example. Outside of the sudoriferous glands, suprarenalin will cause symptoms identical to the phenomenon produced by stimulation of the true sympathetic. This is not to be wondered at, if we remember that morphologically the sympathetic and chromaffin cells have the same origin.

Chromaffin cells, or adrenal cells, or sympathetic cells being of common origin, have a similar function; for this reason the chromaffin system or system of the paraganglia must be classified with the true sympathetic and together with it, belongs to the vegetative nervous system. The chromaffin hormone is not the only one of these substances which acts electively on the nervous systems of the vegetative life. All the glandular secretions of the endocrines act more or less electively on part or the whole of one of the systems. The action is, however, so complex that we as yet do not know definitely how they act. At the present stage of our knowledge, we must limit ourselves to certain definite hormones.

According to their action on the nervous systems of vegetative life internal secretions can be divided into two groups; on one side the secretions of the thyroid and pituitary; on the other, the secretions of the cortex of the suprarenals and of the pancreas.

The internal secretions of the thyroid and pituitary act particularly as stimulants of the true sympathetic, but they only act on certain portions of this system. The thyroid secretions stimulate the superior portions of this system, (cervical and thoracic portion), while pituitrin acts primarily on the vaso-motors and the parts under the control of the inferior mesenteric ganglion.

These two substances are, therefore, partially hypersympathicotonic, and they are also, but to a much lesser extent, hyperparasympathicotonic. The internal secretions of the suprarenal cortex and of the pancreas are exclusively stimulants of the parasympathetic system; they are hyperparasympathicotonic. The suprarenal secretion acts on the tone of the whole parasympathetic, while the pancreatic secretions are limited to the stimulation of the functions having to do with metabolism.

To be complete, we should investigate all drugs and hormones in this manner, but this would be going outside of the field.

If this chapter facilitates the understanding of the following part of the book, I have accomplished what I started to do. Vegetative neuro pathology is still in its infancy and we cannot by a few observations cover all the facts.

CHAPTER XV.

PATHOLOGY OF THE GREATER SYMPATHETIC.

By Dr. P. Harvier.
Physician to the Paris Hospitals.

If we wanted to describe in detail the pathology of the sympathetic, it would be necessary, because of the physiological importance of this nerve, to review a large number of nervous and mental diseases. As Laignel-Lavastine has said:

The pathology of the sympathetic is a border line pathology. To understand this all that is necessary is to refer to a few typical examples. We can, for instance, consider as belonging to the pathology of the sympathetic:

1.—Certain cardio vascular manifestations, such as, tachycardia, bradycardia, arythmia, when the modifications of the rhythm are due to lesions of the nervous system and independent of lesions of the bundle of His; the hypertension crisis described by Pal and Vaquez, the angiospasms, etc.

2.—Thermic and vaso-motor disturbances observed in cerebral hemorrhages (initial hyperemia followed by coolness, then a fall of arterial pressure on the paralyzed side), in medullary traumatism (increase in temperature of the inferior limbs, on the side corresponding to the hemisection, according to the experiments of Vulpian and Schiff).

3.—Trophic disturbances; arthropathies, osteopathies, perforating pain of affections of the cord; hematomyelia, syringomyelia, tabes; indurated edema of hemiplegics and organic paraplegias and peripheral neuritis.

4.—The sudorific disturbances of the same diseases.

5.—Pains caused by alterations of the periarterial sympathetic plexus.

6.—Pilo motor disturbances of nervous lesions.

7.—Cutaneous pigmentations occurring during pregnancy, peritonitis, tuberculosis, enteritis and certain pancreatic affections.

All these pigmentations are due to irritation of the sympathetic.

In the field of mental pathology the sympathetic by its lesions causes disturbances in the circulation of the brain or changes in visceral sensations. Vigouroux and Laignel-Lavastine have shown, for instance, that certain sensations such as a feeling of narrowing of the stomach, œsophagus, etc., found in certain insane individuals were due to chronic lesions of the semi lunar ganglia.

DIVISIONS OF THE PATHOLOGY OF THE SYMPATHETIC.

We will study the pathology of this system according to the following artificial classifications:

1.—The hyperexcitability syndrome of the vegetative nervous system. Sympathicotonia and parasympathicotonia (sometimes still called vagotonia).

2.—The reactions of the vegetative nervous systems in the course of various diseases.

3.—The sympathetic syndromes in their relationship to affections of the endocrine glands or endocrine sympathetic syndrome.

This chapter can be considered as a general pathology of the sympathetic, considered as a nerve-regulating vegetative life.

4.—Localized sympathetic syndromes.

(*a*) Of the cervical sympathetic;

(*b*) Of the mediastinal sympathetic;

(*c*) Of the abdominal sympathetic;
(*d*) Of the peripheral sympathetic.

They constitute the segmentary pathology of the greater sympathetic nerve.

I. HYPEREXCITABILITY SYNDROME OF THE VEGETATIVE NERVOUS SYSTEM.

SYMPATHICOTONIA AND PARASYMPATHICOTONIA OR VAGOTONIA.

Morphological and physiological studies show that the true sympathetic on one side, and the parasympathetic system on the other, have fibres which, from a physiological and pathological point of view, have a remarkable antagonism to each other. Due to the antagonisms of these two systems there results a state of equilibrium. For instance, the heart normally beats at a rate of from 68 to 72 per minute, because the action of the sympathetic counterbalances that of the vagus; in the same manner the action of the pupil is regulated by the action of the sympathetic (dilator) and the parasympathetic (3rd cranial, constriction).

The maintenance of this equilibrium results in the physiological state. Disturbance in equilibrium results in a pathological state. The variation may be in either one of the two systems as a hypo or a hyperactivity. We can, therefore, conceive of pathological disturbances due to hypo or to hypersympathiconia, and again to hypo or hyperparasympathicotonia.

Eppinger and Hess showed a few years ago that it was possible to determine which of the two systems was preponderant, by studying the reactions produced in an individual by the injections of chemicals having a selective action on one or the other nerve.

Suprarenalin injected subcutaneously in 1 gram doses will cause a stimulation of the sympathetic system in certain individuals. This will manifest itself by dilatation of the pupil, a glycosuria superior to 5 grams per 24 hours, after the injection of 100 grams of glucose in the morning, will cause a polyuria, a tachycardia and an increase in the blood pressure by vaso constriction. In other individuals this dose will not cause any changes.

Atropin and pilocarpin have an elective action on the vagus. The first paralyses, while the second stimulates the vagus. The injection of .001 gram of atropin subcutaneously will, in certain individuals bring about a marked reaction. This will manifest itself by a tachycardia, a rapid dilatation of the pupils and dryness of the mouth, due to stoppage of secretions.

The same applies to pilocarpin. In some individuals it will cause abundant salivation, sweating and an increase in intestinal peristalsis.

These differences in susceptibility are due to differences in tonus of the two systems. The latent disequilibrium is emphasized by the preceding reactions to the drugs. In some we can see the predominance of the vagus; these are the vago-tonics, in others we see the predominance of the sympathetic; these are the sympathicotonic.

Thus by means of pharmacological tests, we can explore the vegetative nervous systems and can determine which of the patients' symptoms are due to the vagus and which are due to the sympathetic.

The excitability of the vagus and the sympathetic can also be brought out by mechanical means. By that we mean the oculo cardiac reflex. This was discovered simultaneously by Dagini and Aschner in 1908. It consists in the slowing of the heart rate (6 to 8 per minute) accompanied by a decrease of the arterial pressure, a slowing of the respiration and sometimes nausea, following the compression of the eyeballs. The impulse is transmitted by the branches of the trigeminal and from there goes to the vagus. This reflex is exaggerated in vagotonics (decrease in pulse rate of 10 to 16) while it is absent in sympathicotonics. It may even cause an acceleration of the pulse rate of 20 to 30 beats per minute, without a preliminary decrease.

CLINICAL DESCRIPTION OF HYPERTONIA OF THE AUTONOMIC SYSTEMS.

1.—Vagotonia Predisposition.—Eppinger and Hess have described under this name a constitutional anomaly observed in certain individuals and characterized by a hyperexcitability of the whole vegetative nervous system. It is constituted by signs of both vagotonia and sympathicotonia. Its name is, therefore, rather confusing, and probably a better name for it would be hyperexcitability.

This syndrone is found in young people which in the past we have called nervous. Eppinger and Hess call them nervous system invalids. They consider that they are ambulant patients which report for some trivial ailment which sometimes are referable to the heart or the gastro intestinal tract and which are considered as neurasthenics.

These patients are usually pale, but change color very easily; the hands are often cyanosed, moist and cold and become pale under pressure of the fingers. These individuals perspire easily and these perspirations may be localized to the head, the face or the extremities. When they undress in public red spots are liable to appear on the chest (pudic erythema) and perspiration appears under the arms.

On examination large tonsils are found, a red pharynx and in childhood adenoids. As adults they are subject to sore throat; they often swallow and complain of considerable saliva in their mouth. The pharyngeal reflex is abolished, but this anesthesia should not be considered as a hysterical stigma.

Their respiration is often interrupted by a sigh, followed by a respiratory pause. These individuals often complain of retrosternal discomfort. Examination of the heart reveals a marked irritability. Extra systolic arythmia is frequent, especially after a heavy meal. The pulse rate is usually about 60 per minute. It is characteristically unstable. At the slightest effort it beats more rapidly or in some cases slows down. Respiration influences it greatly. The blood pressure is below normal.

These individuals often have gastro intestinal disturbances. The appetite is good, but there is a sensation of fullness after meals in spite of the fact that the appetite is not satisfied. They have acid eructation and symptoms of aerophagia. They have a tendency to constipation. The reflexes are very rapid. There is often a tremor of the tongue, eyelids and fingers, and a marked dermographia (sign of sympathetic hypertonia). The urines contain large quantities of phosphates. The urinations are frequent and of small quantity. Sexual excitability is frequently exaggerated and shows itself by precocious ejaculation and nocturnal pollution.

2.—VAGOTONIA.—This is much more frequent than sympathicotonia and is found mostly in young people. The principal signs are: Narrow pupils, tendency to bradycardia, or hypotension, respiratory arythmia, palpitation and extra systoles, eructation, aerophagia, gastro intestinal hypersecretion and perspiration.[1]

Vagotonic individuals do not react to suprarenalin, but .01 centigrams of pilocarpin subcutaneously will produce a profuse perspiration. The oculo cardiac reflex is exaggerated. Vagotonia corresponds to an insufficiency of the chromaffin system and co-exists often with an excessive development of the lymphatic system. (status lymphaticus).

3.—SYMPATHICOTONIA.—It manifests itself by: rapid heart, high blood pressure, emotionability, heat waves, slow digestion, dermographism, absence of sweat, goose flesh, febrile reaction.

These individuals are not sensitive to pilocarpin. An injection of adrenalin will produce a marked tachycardia, palpitation, trembling, sensation of cold, high blood pressure, appearance of a glycosuria. Sometimes this action is dissociated and only one of these will manifest itself.

Atropin in doses of .0001 grm. will produce a tachycardia, mydriasis and stoppage of secretions. The oculo cardiac reflex is absent or inversed.

II. REACTION OF THE VEGETATIVE NERVOUS SYSTEM IN THE COURSE OF DISEASE AND VISCERAL AFFECTIONS.

The notion of vagotonia and sympathicotonia brings a new point of view on pathology. It allows us to systematize the symptomatology of functional nervous disturbances. It allows therapeutic deductions of great interest as regards the use of atropin and suprarenalin. Eppinger and Hess have obtained in certain individuals after an injection of pilocarpin conditions resembling well-defined clinical pictures. In the gastro intestinal tract signs of hyperacidity with esophageal cardiac and pyloric spasms, in the lungs, respiratory disturbances simulating asthma. These findings have brought these writers to believe that asthma, pylorospasm, angina, etc., have a common cause in that they are brought about by certain conditions which will act upon the pneumogastric and are observed in vagotonia. The good results obtained in some of these cases by the use of atropin are a proof of an irritation of the vagus.

---

[1] Bauer has observed that there is normally during sleep a periodic physiological vagotonia. The hyperactivity of the vagus is evidenced by a contraction of the pupils, a slowing of the pulse, a tendency to perspire, to nocturnal emissions, an exaggeration of peristalsis, explaining the desire to defecate in most people when they wake up. It enables us to understand also why asthmatic attacks and labor pains occur more frequently at night.

I.—Emotion.—Commotion.—The majority of reflex reactions which characterize emotion do so through the vagus and the sympathetic, visceral, spasticity, trembling, tachycardia, alternating vaso constriction and vaso dilatation, sensation of coolness of the extremities, dermographia, salivation, tears, gastro intestinal and urinary changes.

It is possible that the endocrine glands act on the emotions, as believe the American physiologists, and that the suprarenal glands exert their action by the secretion of suprarenalin which stimulates the sympathetic. Other glands of internal secretion can feel the shock of an emotion.

It is a well-known fact that Basedow's disease can first appear following a strong emotion. Cannon has been able to produce hypersecretion of the thyroid by stimulating the afferent nerves to the suprarenals or by the injection intravenously of a dilute solution of suprarenalin. Emotions are also liable to cause other glandular disturbances, such as, glycosuria, stoppage of menses or of the milk secretion.

Emotion appears as a disturbance of equilibrium of the sympathetic and the endocrines. Certain emotional states, independent of all organic lesions of the nervous system, can be likened to emotion from a physiological and pathological point of view.

II.—SHOCK.—Shock appears in the course of a great many different conditions: Traumatism, hemorrhages, infections, intoxications are primarily nervous reactions, characterized by signs of paralysis or inhibition of the centres of the vegetative nervous systems. State of depression, anxiety, pallor of the face, immobility and often dilatation of the pupils, low temperature, rapidity of the pulse, arterial hypotension, etc. The oculo cardiac reflex is abolished. The vegetative neuro glandular system has a physiological excitation of chemical nature and reacts by a clinical manifestation identical to the different pathological manifestations provoked by the preceding causes. This conception is in accord with the interpretation of traumatic shock given recently by Quenu who believes that this syndrome is due to an intoxication by the toxalbumen arising from the tissues, particularly the crushed tissues.

III.—SEA SICKNESS.—Sea sickness can be considered as a disturbance of equilibrium of visceral enervation. The sensory stimulations brought about by the movement of the ship act both on the vagus (vomiting) and the sympathetic.

Cazamian has shown recently that in the symptoms of sea sickness we find evidence of hyperexcitability of the sympathetic: dilatation of the pupil, arterial hypertension, tachycardia, inversion of the oculo motor reflex.

Sympathicotonic individuals are predisposed to sea sickness while vagotonics are not. Young children do not get sea sick because they are vago-tonic. The use of suprarenalin is illogical while occasionally atropin will give very good results.

IV.—Asthma.—Symptomatic asthma observed in trachio bronchial adenopathy and in aortitis is due to an irritation of the vagus. During an attack definite symptoms of vagotonia are present; increase secretions, slowing of the pulse, dermographia. The attack of asthma is prevented by atropin, paralyzing the vagus, or by suprarenalin stimulating the sympathetic.

V.—Angina Pectoris.—This can be brought about not only by a lesion of the coronaries but also by a nervous lesion, neuritis or neuralgia of the cardiac plexus. Sympathetic syndromes are to be found in the vaso-motor, secretory and pupillary reactions. Certain patients show during the attack extreme pallor, a sensation of coolness, numbness of the extremities with cyanosis, profuse cold sweats, together with a marked dilatation of the pupils. The pneumogastric can also act causing pharyngeal, esophageal spasms and vomiting.

VI.—Tabes.—Visceral crisis of tabes constitute one of the most marked reactions of the vegetative nervous system to lesions of the roots. We can interpret as evidence of a general hypervagotonia: myosis, laryngospasm, paroxysmal abdominal pain, muco-membranous diarrhea, gastric crisis. Rectal, ovarian and testicular crises are evidence of the parasympathetic stimulation.

The work of J. Ch. Roux has brought out the histological lesions of tabes on the sympathetic, which consist of a decrease and even disappearance of the myeline fibres of the sympathetic. It is not to be wondered that these lesions of the sympathetic disturb the equilibrium between the two systems to the advantage of the vagus which causes the symptoms we have mentioned.

VII.—Gastro Intestinal neurosis.—Vagotonia plays an important part in gastro intestinal pathology. It is characterized by motor and sensory disturbances of the stomach, accompanied by phenomena which usually are the results of an irritation of the solar plexus.

These patients nearly always complain of dyspeptic symptoms. These consist mainly in a sensation of fulness. Digestion is slow and there is a tendency to sleep. Outside of the cases associated with ptosis, the size of the stomach is normal. The chemical reaction of the juices will vary and X-ray will not reveal anything abnormal.

These dyspeptic manifestations are accompanied with cardiac, respiratory, vaso-motor and secretory disturbances.

Cardiac symptoms predominate. These consist in palpitations, precordial distress, vertigo, buzzing of the ears, pulsations of the neck and head. The heart is rapid and the arterial tension unstable.

The respiratory disturbances which these patients complain of are characterized by a sensation of discomfort and oppression. The respirations are often interrupted by a sigh followed by a pause.

The vaso-motor disturbances manifest themselves most commonly by vaso-dilatation phenomena; waves of heat, erythema, dermographism or vaso-constriction, coolness, cyanosis, numbness, and a prickling sensation. The secretory disturbances consist of a state of permanent moisture.

This syndrome, more or less complete, appears in the shape of paroxysms caused, either by digestion, emotions or fatigue. Raymond and Carrie consider this as a state of disequilibrium of the sympathetic innervation.

Loeper and Mougeot, basing themselves on pharmacodynamic changes and ocular compression, have shown that gastric neuroses belong either to the vagotonic or sympathicotonic group or to both types. The vagotonic patient is nearly always a young individual having early pain due to cardiac spasm, or late pain due to pyloric spasm accompanied by aerophagia. There is a tendency to hyperacidity. The pulse is as a rule slow and the blood pressure low. These patients also complain of palpitation, angina and occasional periods of asytole.

The sympathicotonic patient shows a certain degree of mydriasis, a tachycardia and a slight arterial hypertension. Digestion is slow, and evacuation of the food from the stomach is slow. Palpitation of the abdomen is painful and increases the dilatation of the pupils and the flushing of the face.

An identical symptomatology can be observed in the course of enteroptosis with colicy spasms, during the course of colitis, and chronic appendicitis. The nervous irritation reaching the coeliac plexus, radiates to the stomach, the heart, the lung and the general nervous system.

Next to functional hypertonia, which according to Hess and Eppinger may lead to ulceration of the stomach by hypersecretion and hyperacidity, we must place organic hypervagotonia which has been particularly studied by Loeper in ulceration of the lesser curvature. We note in the course of this condition, a dysphagia, due to cardiac spasms, a constant nausea, a slowing of the pulse, an exaggeration of the oculo cardiac reflex which is due to the toxins affecting the nerves in the neighborhood of the ulcer.

III ENDOCRINE—SYMPATHETIC SYNDROME.

Clinically, the stimulation of the sympathetic is evident in Basedow's disease and in Addison's disease, and probably also in sclerodermia.

I.—THE SYNDROME OF BASEDOW'S DISEASE.—The characteristic symptoms of Basedow's disease are to be traced either to stimulation of the vagus: sweating, diarrhea, gastro intestinal crisis, simulating tabes, etc., or to stimulation of the sympathetic; tachycardia, tremor, cutaneous pigmentation, glycosuria, etc.

We must remember that Basedow's disease can be present without any goitre. This can only be explained by the irritation of the cervical sympathetic for, experimentally, the stimulation of this nerve causes a vaso-constriction of the body of the thyroid.

The research work undertaken by the Vienna school and that at Sainton, in France, permits us to distinguish two types of Basedow's disease.

Some are vagotonic. They have only a slight tachycardia, but intense subjective cardiac disturbances. Von Graefe's sign is very pronounced (a spasmotic retraction of the upper eyelid). On the contrary, Moebius's sign is absent. There is only a slight exopthalmos. There is considerable perspiration, a gastric hyperacidity, a profuse diarrhea, disturbances in the cardiac rhythm and the absence of an alimentary glycosuria. These patients have an exaggerated oculo-cardiac reflex and react violently to pilocarpin. The others are sympathicotonic. As opposed to the last type, they have a tachycardia. Van Graefe's sign is absent, Moebius's sign is present and exophthalmos is very pronounced. The lacrymal secretions are weak, the skin dry and alimentary glycosuria is often positive. These patients have an absent or reversed oculo-cardiac reflex and react severely to adrenalin.

The exclusively vagotonic or sympathicotonic type is very rare; in the majority of cases the patients suffering from Basedow's disease show evidence of irritability of the two systems. (Sainton, Laignel-Lavastine).

Clinically the syndrome of Basedow's disease appears as an endocrine-sympathetic syndrome, for we have syndromes of Basedow's disease of thyroid origin; the toxic goitre is an example. There are also syndromes of Basedow's disease of sympathetic origin. Laignel-Lavastine and Bloch have observed the syndrome of Basedow's disease, following a pachypleurisy of the apex of the lung involving and irritating the cervical sympathetic. Sergent has found at least signs of it in 5 out of 9 patients suffering from nerve lesions of the cardiac plexus following bullet wounds of the mediastinum. Curschman finally reported a syndrome of Basedow's disease coinciding with gastric crisis in a woman suffering from tabes.

The function of the thyroid can be disturbed just as well by a lesion of the sympathetic nerve as by a glandular lesion.

II.—Syndrome of Addison's Disease.—The part played by the sympathetic in the pathogenesis of Addison's disease is brought out by anatomical, experimental and clinical facts:

(*a*) In the course of autopsies performed on patients dying from Addison's disease, it has been noticed, parallel to the alterations of the suprarenals, a variety of lesions of the sympathetic: compression of the solar plexus by caseated ganglionic masses in the celiac or periaortic region; tuberculosis of the semi-lunar ganglia.

The histological examination brings out, with or without evidence of tuberculosis, a solar ganglia sclerosis, a pigmentation of the nerve cells, a myelin degeneration of the afferent or efferent nerves.

(*b*) Laignel-Lavastine has shown that:

1.—The removal of the suprarenals is followed by lesions of the sympathetic and of the nerve cells of the solar plexus.

2.—The removal of the solar plexus brings about alterations of the suprarenals (hypopigmentation of the suprarenal on the same side as the semi-lunar ganglion removed).

(*c*) Are signs of irritation of the sympathetic;

1.—The pigmentation of the skin in Addison's disease:

2.—The lumbar pains;

3.—The sudden death sometimes of reflex origin, the abdominal pains, sometimes excruciating, the uncontrollable vomiting, the diarrhea, the coolness of the extremities, the hypotension with tendency to collapse, which characterize acute suprarenal insufficiency, resemble the symptomatology which we will describe in the solar syndrome, so much so, that the question comes up if the signs of sympathetic inhibition are not a function of a decreased secretion of suprarenalin, the normal stimulus of this nerve.

When all is said the syndrome of Addison's disease can be considered as a manifestation of a disturbance of the pigmentary suprarenal-sympathetic function.

III.—SCLERODERMIA can be considered as an endocrine-sympathetic syndrome for the following reasons: The theory which considers an endoperiarteritis of the blood vessels as the starting point of the disease is incorrect. We know to-day that vascular lesions are not the result of lesions of the skin.

Raymond claims a nervous origin for sclerodermia, basing himself on the trophic, vaso-motor and secretory disturbances, on the co-existence of a facial hemiatrophy and on the symmetry of the lesions. Brissaud, struck by the location of sclerodermia, considers this disease as due to central medullary or spinal sympathetic root lesions.

There is a tendency to-day to put the blame on disturbances of the endocrine glands: thyroid, and suprarenal. Sclerodermia may follow lesions of the thyroid of rheumatic origin and the treatment with internal secretions has stopped its evolution. Its co-existence with Basedow's disease has been reported several times. In other

cases, the suprarenal intervenes by the production of an excess of suprarenalin. The sclerodermia and the melanodermia which co-exists with it would be caused by an oversecretion of suprarenalin. (Touchard).

IV. LOCALIZED SYMPATHETIC SYNDROMES.

I. CERVICAL SYMPATHETIC SYNDROMES.

This includes Ocular syndromes
Facial hemiatrophy
Migraine

A. OCULAR SYNDROMES.

I.—PHYSIOLOGICAL EXPERIMENTATION.—The cervical sympathetic has two physiological particularities which have a clinical application: 1.—Its vaso-motor action. 2.—Its action on the eye.

(a).—*The vaso-motor action.*—The cutting of the cervical sympathetic or the removal of the superior cervical ganglion will cause a dilatation of the blood vessels, an erythema and congestion of the tissues on the corresponding side of the face, eyes, mucosa of the nose, mouth and tongue. In the rabbit, the ear shows a remarkable dilatation of all the veins in which the blood shows a red color. The local temperature is distinctly higher than on the other side. Stimulation of the sympathetic causes the opposite effect:

1.—A constriction of the blood vessels by vaso-constriction.

2.—A decrease in the local temperature.

(b). *Action on the Eye.*—The cutting of the sympathetic in the rabbit at any one point of its cervical course will cause on top of a vaso dilatation of the back of the eye:

1.—A retraction of the globe of the eye, by paralysis of the muscles of the capsule of Tenon.

2.—A narrowing of the palpebral fissure by paralysis of the smooth muscles of the lids.

3.—A myosis, by cutting off the inhibitory power of the sphincter of the iris.

4.—A decrease in ocular tension.

5.—Late trophic disturbances: conjunctivitis and ulceration of the cornua.

Stimulation of the sympathetic will cause just the opposite:

1.—Exophthalmos.

2.—An increase in the size of the palpebral fissure.

3.—Mydriasis.

4.—A vaso-constriction of the conjunctiva and the iris.

II. Clinical Study.—The sympathetic ocular syndromes clinically show the following characteristics:

1.—Oculo-sympathetic syndrome with stimulation.

2.—Oculo-sympathetic syndrome with paralysis.

3.—Dissociated oculo-sympathetic syndrome.

I. OCULO-SYMPATHETIC STIMULATION SYNDROME.

This is characterized by the following symptoms:

1.—Pallor of the face.

2.—Unilateral pupillary dilatation.

3.—Retraction of the superior eyelid with: increase in size of the palpebral fissure, Von Graefe's sign, the superior eyelid lags behind when the eye looks downwards.

4.—Protrusion of the eyeball or exophthalmos.

II.—OCULO-SYMPATHETIC PARALYSIS SYNDROME.

This is still called the Cl. Bernard-Horner syndrome (for it was first performed experimentally by Claude Bernard in 1858 and observed clinically by Horner in 1869). It is characterized by the following symptoms:

1.—Slight non-paralytic ptosis, due to a narrowing of the palpebral fissure.

2.—Myosis with integrity of the pupillary reflexes.

3.—Enophthalmos.

4.—Muscular hypotonia.

5.—Vaso-motor disturbances (erythema), thermic disturbances (excess of heat), secretory disturbances (sweats) and trophic disturbances of the face and the arm on the same side. Andre Thomas has shown recently in wounds of the cervical sympathetic a weakening of the vascular tone at the level of the corresponding upper extremity, for instance the vaso-motor reactions during a hot bath are less pronounced on the affected than on the healthy side. Oelsnitz and Cornil have made similar reports by means of the study of the oscillary amplitude with the apparatus of Pachon.

ETIOLOGY.

These two syndromes of stimulation or paralysis can be caused by lesions of the cervical sympathetic at various levels. We can consider, from an anatomical point of view, a bulbar centre and a medullary centre (cilio-spinal centre of Budge), localized in the column of Clarke in the first segment of the dorsal spinal cord. The nerve fibres starting from the cord by the rami communicantes of the anterior roots of the first dorsal pairs, reach the cervical sympathetic by means of the subclavian loop.

(*a*) Lesion of the Bulbar Centres.—These cause: either a typical Claude Bernard syndrome or an alternate bulbar paralysis, characterized by a crossed hemiplegia with hemianesthesia, and the syndrome of Claude Bernard with hemiasynergy and lateropulsion on the side of the lesion (syndrome of Babinski-Nageotte).

(*b*) Lesions of the Medullary Centres.—These are better known and are caused by the cilio spinal centre becoming affected in syringomyelia, areas of sclerosis, tabes, hematomyelia, tumors of the cord and its membranes and in medullary compressions (Pott's disease, bone tumors).

(*c*) Lesions of the Rami Communicantes.—The oculo-sympathetic syndrome is quite often observed in lesions of the inferior roots of the brachial plexus.

Since the work of Mrs. Dejerine we know that:

1.—The tearing of the inferior roots alone of the brachial plexus, and especially of the first dorsal nerve, will cause the appearance of oculo pupillary phenomena.

2.—Cutting the 8th cervical and the 1st thoracic at their junction will produce the same effects.

3.—The tearing of the superior roots (6th and 7th cervical) or cutting them at their junction is never followed by ocular disturbances.

4.—The section of the superior or inferior roots of the plexus made 1 cm. beyond their junction does not cause an oculo pupillary syndrome.

This syndrome is, therefore, due to the cutting or tearing of the rami communicantes of the first dorsal nerve which contains motor fibres, which go to the iris; these arise from the cord, pass in the inferior cervical ganglion and travel up by means of the cervical sympathetic to the eyeball. The observation of an oculo pupillary syndrome can, therefore, localize the nerve injury between the cord and the junction of the 8th cervical and 1st thoracic.

(*d*) Lesions of the Sympathetic Trunk and its Ganglia.—The oculo pupillary syndrome is met with in:

1.—Pleuro-pulmonary affections; pleurisy with effusion (Chauffard and Loederich), apex tuberculosis with involvement of the pleura (Souques), apical pleurisy (Sergent), mediastinal pleurisy, syphilitic and tuberculous affections of the mediastinum. We have observed the beginning of a Claude Bernard—Horner syndrome in a tuberculous woman with an artificial pneumothorax.

2.—In cervical and mediastinal tumors.

Diseases of the thyroid (goitres and malignant tumors).

Cervical adenopathy (lymphadenomata, lymphosarcomata).

Neoplastic tumors of the esophagus and the trachea.

Aneurism of the transverse aorta. In this case, the inequality of the pupils is more often symptomatic of nervous syphilis and co-exists with Argyll Robertson pupils, but it can occur alone. The syndrome of Claude Bernard has been reported in several cases.

3.—In vertebral lesions (Pott's disease).

4.—In traumatic lesions (bullet wounds).

(*e*) Reflex Origin.—An oculo sympathetic reflex syndrome has been reported in utero ovarian affections and inflammatory or painful affections of the liver and pancreas.

III. DISSOCIATED OCULO-SYMPATHETIC SYNDROME.

A. EXOPHTHALMIA.

During the course of chronic nephritis with hypertension a slight bilateral exophthalmos is noticed without any other ocular or other signs of Basedow's disease. This is due to an intoxication of the ocular sympathetic in which suprarenalin or analogous substances probably play an important part.

We can also include among toxic exophthalmia certain protrusions of the eyeball, observed during the course of chloroform anesthesia, at the end of the stage of excitation which seems to be due to irritation of the sympathetic and coincides often with a swelling of the body of the thyroid.

B. PUPILLARY CHANGES.

Pupillary changes are noticed:

1.—In nervous affections: pachymeningitis, hemorrhages in the meninges, acute meningitis, myosis precede the mydriasis. During the course of an epileptic convulsion the pupil is dilated and fixed while at the same time the face is pale.

2.—In Basedow's disease the classical authors admit that the pupils are equal. However, Cantonnet has noticed a unilateral dilatation of the pupil in 14 out of 18 cases of Basedow's disease by means of the "provoked mydriasis" test. This consists in the examination in a dark room of the pupils, in from 8 to 15 minutes after the instillation of a 4% solution of cocaine in both eyes.

3.—In pleuro pulmonary affections the modifications of the pupils are important symptoms.

The Claude Bernard syndrome can be noticed as a whole, but it is more often found to be dissociated. On the side affected can be noted: a myosis, a decrease in size of the palpebral fissure, a retraction of the eyeball, the vaso-motor disturbances however are absent. In other cases the oculo palpebral syndrome is absent. There is only a dilatation of the pupil, associated with vaso-motor disturbances of the cheek and of the ear. This may precede mydriasis several months or several years (Sergent).

Finally, inequality of the pupils may occur alone without any ocular or vaso-motor disturbances.

These pupillary modifications in the course of pleuro pulmonary affections are due to two pathogenic mechanisms. Some, such as mydriasis, observed in pleurisy with effusion are of reflex origin, according to the law of Schiff: all peripheral sensory stimulation causes dilatation of the pupil. The others are explained by the anatomical relationship of the sympathetic with the top of the pleura and the mediastinal glands. We must remember that the inferior cervical ganglion and the first thoracic ganglion, whose rami communicantes contain the pupilo dilator fibres, are in direct contact with the apex of the lung.

Depending on whether the lesion affects a part, or all the nerve branches, we notice simple inequality of the pupil, inequality of the pupils associated with vaso-motor changes, or the complete oculo pupillary syndrome.

In apical pleurisy (Sergent), mydriasis characterizes the first stage of pleural irritation and myosis the more extensive involvement.

Fibrous tuberculosis, inflammations of the superior portion of the mediastinum (tuberculous or syphilitic), are always accompanied by a hylum adenopathy. This affects and then destroys the rami communicantes and the sympathetic trunk, whence the appearance of vasomotor disturbances. When the inflammation, spreading upwards, reaches the pupilo dilator fibres, their irritation results in a pupillary dilatation.

IV. FACIAL HEMIATROPHY.

The facial trophic neurosis of Romberg is characterized by the appearance of discolored spots on the face, a thinning of the skin which becomes dry, scaly with an atrophy of the adipose, and muscular tissue and even of the skeleton. It can be caused by a lesion of the sympathetic, or of the ganglia or of one of the centres. Its occurrence, during the course of syringomyelia, is considered by Dejerine and Mirallie to be due to a destruction of sympathetic fibres in the cervical cord. L. Jacquet has observed it during the course of a pleuro pulmonary tuberculosis, affecting the inferior cervical ganglion. The co-existence of the facial hemiatrophy, with oculo pupillary disturbances, and sclerodermia has been noted by many writers. It has been seen after operations on the greater sympathetic on epileptics. Finally, Brown-Sequard and Angelucci have observed experimentally, atrophy of the face and of the bony cranium following the extirpation of the superior cervical ganglion.

C. CERVICAL SYMPATHETIC SYNDROME IN MIGRAINE.

The vaso-motor and sensory disturbances which are found associated with attacks of migraine have for a long time attracted attention, so much so that migraine has been divided into two groups: White or Sympathicotonic migraine, characterized by pallor, coolness of the face, dilatation of the pupil, and marked pulsation of the temporal artery which appears tortuous and sinuous on the painful side, and red or sympathico-paralytic migraine, with redness of the face and ears, sensation of heat and an increase in the local temperature, enophthalmia, myosis, nasal and lacrymal hypersecretion. Jaccoud associates these two types and has described a mixed form with two successive phases (white at first, red in the end). While Dubois Raymond considered migraine due to a stimulation of the cervical sympathetic, Mollendorf looked on it as a paralysis of the nerve. Axenfeld considered its starting point at the level of the cilio spinal centre, that is, in the cord itself. We know that disturbances of the sympathetic innervation (digestive disturbances by irritation of the solar plexus, genital disturbances by means of the pelvic plexus) are capable of bringing on an attack of migraine.

II. MEDIASTINAL SYMPATHETIC SYNDROME.

This has been described by Sergent and his pupils, Pruvost and Labro, in patients having bad wounds of the chest and complaining of thoracic pain, and oppression at the slightest effort, in which the most careful examination failed to reveal any cardiac or pulmonary lesion. In these cases, however, it was possible to find symptoms which could only be interpreted by a lesion of the sympathetic or the pneumogastric. These were: Disturbances of the respiratory rhythm, a disturbance of the oculo cardiac reflex (usually reversed), an irregularity of the pulse with or without arrhythmia, pupillary disturbances (inequality, instability, etc.); finally vaso-motor and sudoral disturbances of the face and arms. Quite frequently could be found at the same time disturbances pointing to a hyperfunction of the thyroid; the gland enlarged, the eyes protruded slightly; there was a slight tremor of the hands and a certain amount of moisture of the skin.

This syndrome of Basedow's disease is explained by the following physiological facts concerning the action of the sympathetic on the thyroid. Fr. Franck and Hallion have shown the definite vaso-motor action of the nerve on the gland. Morat and Briare have determined that if the stimulus is applied below the inferior cervical ganglion, this is followed by a vaso-dilatation of the thyroid. This is due to the irritation of the vaso-dilator fibres of the thyroid coming from the cardio aortic plexus (Fr. Franck and Hallion).

To the symptoms of vagus-sympathetic stimulation are added sometimes symptoms due to a lesion of the phrenic nerve (special painful spots, dyspnea caused by effort, immobilization of the diaphragm on the affected side).

The X-ray in certain cases reveals a foreign body at the level of the base of the heart in the zone of the cardiac plexus. If the projectile has gone through the thorax, it is possible to believe that it has injured the nerves on its way and in this case the syndrome clears up as the nerve fibres recover.

III.—ABDOMINAL SYMPATHETIC SYNDROME.

SOLAR SYNDROME.

I. PSYSIOLOGICAL EXPERIMENTATION.

The physiology of the solar plexus has been studied by Courtade and Guyon, Hallion, Laignel-Lavastine. This plexus controls: 1.—The vaso-motor phenomena of the viscera; stomach, intestines, liver, spleen, pancreas and suprarenals; 2.—The motor phenomena of the gastro intestinal tract; 3.—The secretions of the digestive glands.

The work of Laignel-Lavastine has shown that:

1.—Stimulation of the Solar Plexus causes a violent epigastric pain, an intestinal paresis, (constipation), an increase of the arterial tension by an intense abdominal vaso-constriction.

2.—Removal of the Solar Plexus will cause symptoms of paralysis of variable intensity:

(*a*) A hyperacute syndrome, characterized by a marked drop in the blood pressure: a very small and very rapid pulse, coolness of the extremities, vomiting, a bloody diarrhea, anurea. The animal dies rapidly in collapse.

(*b*) An acute syndrome, characterized by similar symptoms, but not as severe: rapid pulse, bloody diarrhea and death in from 4 to 5 days. At autopsy, there is a marked hyperemia of the visceral organs, liver, spleen, lung, stomach, intestines, suprarenals (particularly the medullary portion), while the kidneys are normal. We know that the fibres of each of the splanchnic nerves which go to the kidney do not go through the corresponding semi lunar ganglion (Laignel-Lavastine).

(*c*) *A Subacute Syndrome.*—Some animals survive the operation after showing severe symptoms. These consist in diarrhea, rapid and weak pulse, oliguria and dysuria.

(*d*) *A Chronic Syndrome.*—This will go on for several months and may be compatible with a state of perfect health. "The regulating function exerted by the solar plexus can be more or less compensated." (Laignel-Lavastine).

II. CLINICAL STUDY.

1. SUPERACUTE SYNDROME.—The patient is taken with a sudden excruciating epigastric pain in the deep periumbillical region, sometimes even vertebral; this is accompanied either with a sensation of constriction or of something going right through the body. The patient screams and cannot move.

Then he begins to vomit; at first food, then fluids, then bile, and this is followed by distensions of the abdomen and bloody diarrhea.

At the same time severe general symptoms appear, coolness of the extremities, subnormal temperature, weak, rapid pulse, fall in blood pressure, anuria and collapse.

The patient dies very shortly.

The clinical picture is that of a virulent peritonitis or of an acute gall stone crisis.

2. SUBACUTE SYNDROME.—The onset is sudden, sometimes following an effort. The patient complains of a severe pain in the region between the sternum and the umbilicus, and simulates a spasm of the stomach, which radiates to the back and both shoulders. This is followed by vomiting, often fetid diarrhea. The pulse is weak, the urines rare. The attack subsides after a time, but repeats itself.

3. CHRONIC SYNDROME.—1. *Neuritis of the Solar Plexus.*—This is characterized by abdominal pains. These start as a rule as isolated attacks, but soon become continuous with paroxysms. These pains are spontaneous and have

no relation to meals, or movements, differing in this way from gastric ulcer or stones in the kidney.

The pain is frankly epigastric (it occasionally starts at the level of the 11th and 12th ribs on the left side, then gradually localizes on the median line), radiates towards the thorax, the back and the shoulders.

These paroxysmal attacks, lasting longer and longer and often becoming more and more painful, end up by a state of visceralgia or of constriction around the waist. These patients have a characteristic attitude: they sit down, bend forwards with the knees flexed.

No food can be tolerated during the attacks. Vomiting is frequent and in the intervals between the attacks the patients complain of a sensation of abdominal distension.

2. *Coelialgia.*—The stimulation of the nerves of the solar plexus manifests itself by abdominal painful spots the topography of which has been studied by Loeper and Esmonet and which can be brought out by means of the esthesiometer of Roux and Millon, or by a moderate pressure of the finger.

These painful spots are above, at, or below the umbilicus.

Painful spots above the umbilicus are common in gastric affections. One is the epigastric spot, at the lower limit of the upper third of a line from the umbilicus to the xyphoid. Pressure at this spot will sometimes bring out a corresponding painful spot on the spine. Another point, called the solar point, corresponds to the lower limit of the middle third of the segment on this line, and corresponds to the coeliac region and to the solar plexus itself.

The para umbilical spots are found nearly always in intestinal affections. There is a superior mesenteric spot and an inferior mesenteric spot, which correspond to the origin of the two mesenteric arteries of this name.

The spots under the umbilicus are: 1.—The promontory spot, at the point of junction of the sacrum and the spinal column; 2.—The iliac spot, corresponding to the bifurcation of the iliac artery into its two branches, internal and external iliac, located at the bisectorline of an angle formed by a line uniting the umbilicus to the anterior superior iliac crest and by a line which unites the two anterior superior iliac crests at 4 cm. of the median line; 3.—Lanz point, at the union of the external and middle third of the bi-iliac line. MacBurney's point, located at the middle of the unbilical iliac line on the right side. These last two points correspond to the appendix.

Coeliac neuralgia gives rise to paroxysmal attacks either gastric or intestinal.

The gastric crises which manifest themselves by dyspeptic disturbances: anorexia with gastric intolerance, resemble those of tabes. The enteralgia crises manifest themselves by attacks of diarrhea with occasional entero colitis.

III. ETIOLOGY.

The solar syndrome has many causes:

1.—Peritonitis.—Whether we are dealing with acute peritonitis, by perforation of a gastric ulcer or subacute (post operative or by obstruction), of chronic peritonitis (tuberculous or alcoholic), the solar syndrome is determined not by the inflammation of the peritonium itself, but by lesions of the solar plexus or its terminal ramifications. Peritonitis is to the solar plexus as meningitis is to the cerebral cover and the sympathetics express the pain of the nerve elements. In acute peritonitis the parenchymatous lesions predominate: the nerve cells are swollen and show signs of degeneration. In certain cases, there is a disappearance of the nerve cells. In the chronic forms there is noticed a leucocytic invasion of the solar ganglia, sclerosis and pigmentation of the nerve cells. (Laignel-Lavastine).

2.—ACUTE AND HEMORRHAGIC PANCREATITIS.—The acute symptoms of paralysis are observed at the beginning of this condition.

3.—CHRONIC PANCREATITIS, particularly cancer of the body of the pancreas (Chauffard) with or without peripancreatitis, the diabetic pancreatitis (Loeper) constitute the most important causes of neuritis of the solar plexus as well as:

4.—GASTRIC AND PERIGASTRIC LESIONS OF THE LESSER CURVATURE AND THE POSTERIOR SURFACE OF THE STOMACH. (A. Mathieu): ulcer, ulcerated cancer or cancer.

The solar plexus during the course of the affections just mentioned is irritated and compressed either by adhesions in the neighborhood of the ulcer (perigastric), or by inflammatory or neoplastic adenopathy secondary to gastric or pancreatic lesions.

5.—INTESTINAL CANCER (of the small intestines and propagation in the mesentery or the colon) give rise to two kinds of nerve lesions: Some inflammatory, when the tumor is ulcerated or infected, characterized by a lymphocytic infiltration, a proliferation of the capsule of the nerve ganglia; some cancerous lesions, a real carcinomatous involvement of the intra intestinal nervous system by propagation from a ganglion or a lymphatic in the neighborhood of the neoplasm or by direct propagation of the cancer by means of the nerve according to a mechanism studied recently by Loeper and comparable to the ascending radiculo neuritis of tabes and other infections.

6.—INTESTINAL AFFECTIONS.—Typhoid fever, dysentery, certain severe colitis produce certain inflammatory lesions of the intestinal nervous system (entero neuritis of Loeper). The close bonds which unite the nervous system of the intestines and the coeliac plexus, allow us to believe that an entero neuritis can propagate in the abdominal nerves and the solar plexus and give rise to coeliac alterations which explain the solar neuralgias, sometimes persisting after infectious lesions of the intestines.

7.—TUBERCULOSIS.—Mucous membranous entero colitis, frequent in tuberculous individuals, the enteritis and tuberculous peritonitis with mesenteric adenopathy, the lesions of the suprarenals, accompanied by caseated or sclerous perisuprarenalitis, compress and irritate the branches of the sympathetic. At autopsy there is noticed, depending on the case, either tuberculous lesions of the solar plexus, or ordinary inflammatory lesions with adhesions to the neighboring organs. The nerves of the solar plexus can also fix toxins and even tubercle bacilli and the coelialgia has then a toxic neuritis or a bacillary cause.

8.—GENERAL TOXIC INFECTIONS.—The solar plexus reacts to toxic infections as do other tissues. In the course of general infections, pneumonia, small pox, streptococcus and typhoid septicemia lesions occur, the nature of which vary with the duration of the disease: degenerative lesions of the nerve cells in virulent infections; nodular lesions (vascular dilatation and leucocytic infiltrations) in subacute infections, sclerous lesions in the slower forms.

The solar plexus follows the general anatomical and pathological rules. Experimentation reproduces these different types of anatomical disturbances, either through poisons, such as, the diphtheria toxin, by means of mechanical or chemical agents, or as the result of bacterial infections (colon bacillus, typhoid bacillus, streptococcus). (Laignel-Lavastine).

It is thus that a certain number of entero neuroses following typhoid, and scarlet fever and influenza, are due to inflammatory or sclerous lesions of the solar plexus.

IV. DIAGNOSIS.

Whatever the form, acute, subacute or chronic, the solar syndrome is characterized chiefly by paroxysmal attacks of pain accompanied by gastric intolerance, vomiting and occasionally diarrhea.

We must differentiate them from the other painful abdominal syndromes:

1.—Gall or kidney stone crises. These are usually easily localized after a patient has been under observation for some time.

2.—Slow intestinal stenoses, only rarely give rise to sharp pains.

3.—The gastric crises of tabes resemble very much solar syndrome. Between the attacks, however, all painful sensation disappears, while there is still a vague pain between the attacks in solar crisis. The diagnosis is usually made by the observation of the clinical signs of tabes and the examination of the spinal fluid.

Once the solar syndrome is recognized the cause must be determined.

1.—Chronic ulceration or cancer of the lesser curvature must be looked for, by the examination of the gastric contents, the determination of blood in the stools and X-rays.

2.—A pancreatic lesion can be suspected when there is severe pain over the pancreatic spot described by Chauffard and Rivet, two fingers above and to the right of the umbilicus, on a line bisecting the angle formed by the median line and a horizontal line passing by the umbilicus. The alimentary glycosuria test, the examination of the feces and the determination of fat will help to make the diagnosis.

3.—In certain cases all clinical investigation is negative. In an intermittent painful abdominal syndrome in which the diagnosis of tabes, or organic gastric lesions or of lesion of the pancreas cannot be made, the cause of the syndrome cannot be found. These cases correspond to the coeliac neuralgia of Friedrich and the mesenteric neuralgias of Nothnagel.

V. TREATMENT.

In the organic lesions of the stomach and the pancreas these solar crises lead in general, to an intense and rapid cachexia which is not only due to the carcinomatous condition, but also to the fact that the patients do not eat, and sleep very little. In this type of syndrome, there is very little to be done. Even morphine, in ever-increasing doses, is of little avail and surgical interference is the only help.

In the case of inflammatory gastric lesions, the liberation of adhesions is often followed by improvement. Even in cancer of the body of the pancreas, certain surgeons do not hesitate to remove the solar plexus and the semi lunar ganglia. Chauffard has reported several observations in which the patients ceased to suffer for a certain length of time, when nothing was done, in presence of the neoplasm, except an exploratory laparotomy. The question comes up if the cessation of pain was not the result of suggestion (Mathieu). The important thing, however, is the fact that the patient feels relieved.

REFLEX SOLAR SYNDROMES.

Sudden death may be caused by violent traumatism, such as, a blow in the epigastric region. It has been also reported following the ingestion of a glass of ice water acting on the stomach as a traumatism. Death by stoppage of the heart, following certain painful syndromes, such as, hepathic colic has also occurred.

A contusion of the solar plexus is only occasionally followed by slowing of the pulse

These facts can be compared to the modifications of the radial pulse following stimulation of the abdominal sympathetic (solar plexus and nerve endings), described by Andre Thomas and J. Ch. Roux under the name of the "hypotensive coeliac reflex." The direct stimulation of the solar plexus by moderate compression, even painless, causes a marked weakening of the pulse, particularly in neurasthenics, of various sorts. The same reflex is observed, but in a less marked degree, in patients suffering from organic affections of the gastro-intestinal tract, following the exploration of the inflamed and painful viscera.

GASTRIC CRISIS.

All gastric crises may be considered as the expression of a crisis of hyperesthesia of the solar plexus, leaving out of consideration the possible etiological factor.

Outside of the gastric crisis of tabes it is possible to find gastric crisis following herpes (Camus and Baufle).

Ulcers of the lesser curvature manifest themselves sometimes by paroxysmal pains identical, from a clinical point of view, to the crisis of tabes. (Tabeform crisis studied by Babinski and Enriquez).

The starting point of the pain reflex is at the level of the fibres or fibre ganglion lesion in tabes, while in ulcer the starting point is at the level of the stomach and is brought about by alterations of the fibres of the sympathetic and vagus.

ENTERALGIA IN LEAD COLIC.

The periumbilical and epigastric pains of acute lead poisoning, the constipation, the increase in blood pressure (hypertensive crisis) are a real syndrome of stimulation of the solar plexus (Laignel-Lavastine).

MUCO MEMBRANOUS ENTERO COLITIS.

This affection is characterized by three cardinal signs: constipation, the presence of muco membranes and painful crisis and are really an enteralgia of the abdominal sympathetic. A. Mathieu has brought out the fact that in this disease it is possible to illicit the various painful points of the solar plexus. While there is spasm of the colon, the maximum pain is near the umbilicus and can even be from 1 to 2 c.m. above it. The umbilical and superumbilical pain is more marked when the examination is made during the course of one of these painful attacks.

"The intensity of the crisis," says Mathieu, "is measured by the intensity of the pain on palpation in the median line of the abdomen between the xyphoid and the umbilicus."

Next to muco membranous entero colitis can be considered as closely allied from a pathological point of view, the painful intestinal attacks observed in uremic or oxalic, or gouty patients (Loeper), the probable cause of which is impregnation of the plexus with toxic substances.

IV. PERIPHERAL SYMPATHETIC SYNDROMES.

The following affections can be considered as such: Raynaud's disease, erythromelalgia, angio-neurotic edema and periodic intermittent hydrarthrosis. While the pathology of these conditions is still hypothetical the interference of the sympathetic does not appear to be doubtful in the etiology of the vaso-motor disturbances which characterize them.

1. RAYNAUD'S DISEASE.—This condition can be divided into three stages: local anemia, asphyxia or gangrene of the extremity. This is an angiospastic affection. Raynaud considers this disease to be due to an extreme irritability of the vaso-motor centres in the cords.

According to him, due to a cold or to certain endogenous toxins, there is produced a reflex vaso-constriction, the intensity of which determines either syncopy, or asphyxia or gangrene of the extremity. Vulpian claims that this vascular spasm can be explained by an affection of the ganglia in the course of travel of the vaso-motor fibres which accompany these vessels.

2. ERYTHROMELALGIA.—This affection was described by Duchenne of Boulogne, then by Weir Mitchell, and is characterized by painful swelling of the extremities accompanied by a reddish discoloration and an elevation of the local temperature. It may be considered as just the opposite to Raynaud's disease, a vaso-motor paralysis of the extremities, resulting either in an inhibition of the excito motor stimulation from the medullary centres or of a direct or reflex modification of the juxta vascular sympathetic ganglia.

The observation of Lannois of a woman first suffering from erythromelalgia, then of the syndrome of Raynaud, following cerebral lesions with destructive lesions of the cells of the column of Clarke at the base of the posterior horn, allows us to bring these two syndromes together and to interpret them as two opposed manifestations of an alteration of the sympathetic centres.

3. ANGIO-NEUROTIC EDEMA.—This is characterized by the appearance of circumscribed tumefactions of the skin and subcutaneous tissue and occasionally affects the

mucosa. It is due to a paralysis of the vaso-constrictor nerves or to a stimulation of the vaso-dilators of central or peripheral origin.

Chronic angio-neurotic edema (Meige) acquired or congenital, familial or individual is believed by Sicard and Laignel-Lavastine to be due to an alteration of the sympathetic, causing an exaggerated transudation of the lymph in the subcutaneous tissues.

4. INTERMITTENT PERIODIC HYDRARTHROSIS. — The majority of writers consider this to be a motor neuritis. In some cases it is believed to be due to thyroid insufficiency.

ORGANO THERAPY.

PHARMACOLOGICAL FACTS.

By H. Carrion.

Former Chief of Laboratory of "l'Assistance Publique" at the Saint-Antoine Hospital.

We include under this all animal products utilized as medications, be they furnished by a gland of internal secretion like the thyroid, or a gland of external secretion like the pancreas, or obtained from a non-glandular substance like muscle extract.

As a general rule, we employ the organs of healthy and normal animals. In certain cases, however, we utilize animals which have been intentionally modified physiologically. For instance, Ballet and Enriquez have utilized for the treatment of hyperthyroidism, the blood of animals deprived of their thyroid for a certain time by means of a surgical interference. Carnot and Deflandre have conferred hemopoitic properties on the serum of certain animals by means of repeated withdrawals of blood and have utilized it in the treatment of anemias.

In reality, all serums employed in therapeutics could be considered as a separate subject and included under the title of "serotherapy."

PHYSIOLOGICAL BASIS OF ORGANO THERAPY.

Certain general considerations are the basis of organo therapy and it is well to keep these in mind.

One of the most important facts to remember is the specificity of organs, not only from a functional and anatomical point of view, but also chemically. Each organ is made up of certain definite substances which are particular to it.

Hallion has particularly insisted on this point. "There certainly exist a number of specific cellular products. These are at least as many as there are organs: The color, the characteristic smell of each organ,—which superimposes itself in mammals to the smells of the zoological species—would be sufficient to prove this, without speaking of the physiological effects which investigators have found in a certain number of these extracts. There are also in some organs, if not in all, several specific substances."

This alone would allow us to believe that there are certain determined properties which are specific to certain organs and which may be taken advantage of in therapeutics, just as this is done in the case of certain plants. It is not, however, from this idea that organo therapy, as we understand it to-day, was born; it emanates from the conception of the internal secretions of Claude Bernard and particularly to its generalization by Brown-Sequard.

We know how this celebrated physiologist reaches the conclusions that not only certain glands, but the greatest variety of organs were able to elaborate, within their cells, certain substances which were afterwards poured in the blood stream. Each one of these products has a definite action on other organs. These products are specific in different ways. By their origin, as they come from one well-defined organ, by their chemical composition and by their physiological action.

From this conception we see that the absence or deficiency of a certain organ, results in the deficit of one or more useful substances, often absolutely necessary. The rational procedure in this case would be to introduce in the organism these substances which are missing. The logical way to obtain these substances would naturally be in similar healthy organs.

As we introduce into the gastro intestinal tract pepsin, pancreatin and other similar ferments, to make up for a deficiency of certain external secretions, so an attempt is made to introduce into the organism, by means of injection or ingestion, certain products of internal secretion, the absence of which is causing a variety of disturbances.

Another important fact has been a great help to modern organo therapy, that is, the elective action of the extracts of an organ, on this same organ.

The mode of action of organo therapy can, therefore, be brought about in several ways.

MODES OF ACTION OF ORGANO THERAPY.

From what we have just said, we see that organo therapy can be looked at as a substitute method, a stimulating method and finally, as a purely symptomatic method.

Organo Therapy as a Substitute Method.—As was the conception of Brown-Sequard we have seen that medication by means of the extract of organs could be used to replace a more or less deficient function of an internal secretion. Any organ, being the specialized manufacturer of a useful circulating substance, the pathological decrease, and still more, the suppression of this organ must deprive the body of its products; from this local disturbance must result an effect on the whole organism and particularly certain other organs which acts functionally with the affected organ.

From this physiological disequilibrium may arise a variety of troubles, more or less intense, depending on the importance of the internal secretions which have been decreased or suppressed. These disturbances are varied, since the organs secondarily affected by this deficiency also have their secretions more or less modified.

Organo therapy, considered as a substitute method, acts by obtaining from a healthy organ the various products which are manufactured in decreasing quantity by the damaged organ; and introducing these products into the organism, in other words, substituting the deficient internal secretion.

It is evident that this is a logical point of view and is justifiable. All that is necessary is to recall the wonderful effects of thyroid medication in the human or in the animal whose thyroid has been destroyed or atrophied. All the extracts of organs, it is true, have not such a wonderful substituting action as the extract of thyroid, but this difference is understood when we consider how essential the function of the thyroid is. If a similar function exists in all organs it is certain that it does not present the same general utility. Some can be disturbed without causing by their deficient secretions any severe disturbances; in these cases, organo therapy, while still accomplishing good results, would not be as spectacular.

When all is said, we must admit that the function of internal secretion belongs to a certain extent to all organs; it seems logical to believe that in regard to all the organs, organo therapy, from a theoretical point of view at least, can act as a substitute.

This mode of action has also been called direct action, for it acts directly on the organs secondarily affected, without the interference of the one which is primarily the cause. This term, however, is less significant, as it might apply also to the direct action on the diseased organ.

ORGANO THERAPY BY STIMULATION OF THE ORGAN.—An extract of an organ not only supplements the action of the internal secretion of the corresponding organ but it also acts on the organ itself. Gilbert and Carnot have brought this out as regards certain organo therapeutic medications. They have shown it, in particular, in the case of the liver which is stimulated by extracts of liver.

If this gland is slightly affected it is stimulated; if, however, it is very much degenerated, the extract of liver remains inactive, just as digitalis becomes inactive when the myocardium becomes affected. By this mechanism we can explain the action of most of the glandular extract. "An extract of an organ, given in proper doses," says Hallion, "stimulates electively, in the subject receiving it, the functions of the organ of the same name."

This law appears to be general. It is thus, as the last-named authority has shown, that this same law applies to the extract of thyroid, the most perfect type of internal secretion having a substitute action. "It has been shown that outside of its function as a substitute to the deficient thyroid, it also acts on the remaining thyroid as a stimulant which can be explained in the following manner: Thyroid extract contains a variety of specific substances. These are, independent of the colloidal material, the substances which only the thyroid can manufacture and which it utilizes to build up its own protoplasm or manufacture its secretions. When these substances are introduced into the circulation, it seems as if the thyroid recognizes them; it takes hold of and utilizes them—since they are received already made up—either to repair its own structures or to help it to functionate."

One of the most definite demonstrations of this was shown by Ballet and Enriquez. They caused the appearance of Basedow's syndrome by the injection of thyroid extracts and obtained a hypertrophy of the body of the thyroid which, microscopically, showed stimulation and hyperplasia. Renon and Arthur Delille, by using smaller doses in rabbits, were able to show on histological examination of the gland a marked increase of colloidal material secreted in the vesicles.

Other organs act in the same manner as regards their extracts.

Caussade and later Oppenheim caused a marked hypertrophy of the suprarenal capsules by repeated injections of extracts of these glands. The organs became from 4 to 6 times as large as normal, in similar experiments carried out by Loeper, on guinea pigs and rabbits.

Babes and Jonesco were able to obtain an increase of anywhere from 10 to 30 times the weight of the organ.

Pituitary extract, administered to rabbits by Renon and Arthur Delille, caused also a hypertrophy of that organ and particularly histological changes showing an increased secretory activity. Hallion and Alquier obtained similar results. Guerrini has reported analogous findings.

The pituitary, the suprarenals, the thyroid which are particularly characteristic, vascular organs are not the only ones which manifest this phenomenon. Frouin surgically isolated the stomach of dogs from the rest of the gastro intestinal tract and measured the quantity of gastric juice secreted. By injecting in these animals gastric juice (previously neutralized so as not to cause any irritation), there was an increase in the gastric secretion; the same results were obtained if gastric juice was absorbed by the intestines—this fact, by the way, demonstrates the efficacy of organo therapy by ingestion.

Similar facts have been shown with the mucosa of the duodenum. It is a well-known fact that Bayliss and Starling discovered in the duodenal mucosa a substance: secretin, which when injected in the blood causes an increase in the secretion of the pancreas, the liver and the intestines. Enriquez and Hallion have shown that this substance was in living animals secreted by the duodenum as an internal secretion. (This fact was believed but never proved by the English physiologists). Experimental facts also led them to believe that this substance had an elective action on the duodenal mucosa.

Carnot and Deflandre have shown on their side that tissues in formation or regeneration secrete substances which stimulate the activity of similar tissues. For instance, fetal bone marrow causes medullary hyperplasia in anemias.

From these experimental facts we are lead to believe that this is a general rule for all the organs, and, if it is so for healthy tissues, it is reasonably also probable in diseased organs which have become impaired.

We must remember that cells, in order to functionate and repair their own structures need special products which they manufacture themselves from various substances brought to them by the blood stream. Sick or decreased in number, these same cells have their work made easier if the various products which they need are brought to them all made up.

Whatever the interpretation, there is one important fact from a practical point of view; that is, the elective action exerted by the extract of an organ on a similar organ. This fact has been proved experimentally and clinically. Organo therapy is greatly helped by this fact.

From this also result certain counter indications; when an organ is defective by hypersecretion, the use of a homologous internal secretion must be forbidden. This fact is well known; all we have to do is to remember the action of thyroid in hyperthyroidism which in nearly every case gives very bad results. There are, to be sure, certain contradictory reports on this. Certain cases have been reported which seemed to improve after receiving small doses of thyroid. It is not impossible that a physiological product might have a regulating action and, therefore, capable of bringing back a disturbed functional equilibrium in one way or another. Other interpretations could be given, but for the present it is sufficient to say that such results are exceptional.

ORGANO THERAPY AS A SYMPTOMATIC MEDICATION.—To supplement a diseased organ in its secretory function, or to restore it to its integrity, the clinical study of the symptoms is naturally necessary. To bring out the factor or to treat a symptom, we can also proceed by symptomatic medication.

Certain symptoms or syndromes are justifiably treated by organo therapy, whatever their initial cause; for instance, in capillary hemorrhage of traumatic origin; suprarenalin applied in situ, or injected subcutaneously or intravenously will remedy this condition, thanks to its vaso-constriction power.

There is no question in this case of influencing the suprarenal capsule. We are using a medication which we know, empirically will remedy the symptom.

The same holds true in certain affections characterized by complex clinical symptoms which have not been demonstrated to be of endocrine origin. For instance, suprarenalin or pituitrin, or better still, a combination of both is very efficacious in stopping attacks of bronchial asthma. This does not mean that asthma is due to a deficiency of the pituitary or of the adrenals. We are using these medications against a certain syndrome which we know empirically will be improved by it. These are purely symptomatic medications, the mechanism of which is still obscure.

We could multiply these examples many times, but the ones we have mentioned are sufficient to show that organo therapy can be employed when there is no internal secretion deficiency, in the same manner as we employ vegetable or chemical drugs in the treatment of various conditions.

THE PREPARATION OF THE VARIOUS PRODUCTS USED IN ORGANO THERAPY.

The various organo therapeutic products can be administered fresh, or as complete or partial extracts of these substances.

Fresh organs require a minimum amount of preparation. In the majority of cases the substance is made up of a pulp of the fresh organ. In this manner, fresh liver in particular, is prescribed in large doses. In other cases, the patient is given a maceration of the substance in normal saline; finally, it is possible to have the patient take the fluid products (bile, blood), either as they are, or coated to avoid the action of the digestive juices.

Off hand, we might think that preparations of fresh organs would be the best way to administer these products, since they would be ingested without any modifications and would contain a maximum of the qualities found in the living organ. This consideration, however, is of very little importance. By certain procedure it is possible to obtain the various substances found in these organs without in any way deteriorating them. Furthermore, in a dead organ chemical changes occur very rapidly, while by the methods employed in drying, the active principles can be kept stable and indefinitely. This is a fact, which has been verified by histologists and chemists as well as by physiologists.

If the use of fresh organs has no special advantage, it has, however, certain inconveniences. Carnot remarks that from a psychological point of view the patient will not have much faith in a medication which comes from the butcher instead of from the druggist. Without berating the value of this statement, there are other facts, however, in favor of prepared products.

First of all, we must take into account the disgust of the patient for raw products, however we may disguise the smell and the taste.

In the second place, it is possible that the so-called fresh substance may not be so. Seasons play an important part. For instance, warm weather makes it very hard to keep visceral organs. Furthermore. we do not know how long the animal has been dead.

It is rather difficult to make a pulp of the organ, especially when it cannot be cooked.

We must also remember the possibility of anatomical error due to ignorance, in which case the patient is likely to get thymus or submaxillary gland instead of thyroid. Finally, as Hallion has pointed out, the fresh gland from a different animal every day will show individual variations of activity and toxicity which are not to be found in dry extracts. These are made up of a mixture of glands from many animals and in this way the product is about the average.

It is, therefore, rational, except in very rare cases (gastric juices for instance) to use dried extracts.

These can be in total or partial.

The total extracts are simply dried powders containing the total of the active bodies of a certain organ. Partial extracts are rarely employed. They are usually made up of parts of an organ which are different anatomically from each other (the pituitary for instance from which the posterior lobe can be isolated) or when an attempt is made to isolate the active principle of a gland (suprarenalin extracted from the medullary portion of the suprarenals). The differentiation is, however, rarely possible so that the examples given are practically the only ones so far which can be so obtained. Furthermore, it is questionable if it is advisable to use partial extracts.

We must admit then when we are trying by means of organo therapy to make up the deficiency of an organ, this organ is nearly always in a state of hypofunction of all its products. It can be imagined that only one of the functions will be affected. In these cases the affected organ will only take the secretion which it needs. Finally, when we only administer part of an organ we perhaps prevent the patient reaping the benefit of the substances contained in the parts which are not administered and which probably help to keep up a certain equilibrium which we should avoid disturbing.

This holds not only for partial extracts, but still more for the definite products which we have isolated from certain organs. To be sure, there are only two of these so far, namely, iodothyrin and suprarenalin.

Iodothyrin is not a chemical compound of definite structure, for its iodine content varies and this is probably also true of its activity. One fact is certain and that is that there is no advantage in giving iodothyrin instead of the total thyroid extract.

Suprarenalin is a definite product; it has not only been isolated but made synthetically. It is true that this synthetic suprarenalin can be used instead of the total extract of the suprarenal gland in certain cases. It still holds, however, that this substitution is not advantageous in all cases. Suprarenalin is easier to measure and preferable for local applications and in certain general indications. It is best, however, in treating endocrine disturbances to use the total extract of the gland containing not only suprarenalin but other substances, the nature of which is still unknown to us, but whose value physiologically and therapeutically is undeniable. Suprarenalin is the only one of the internal secretions which we have been able to determine so well.

The preparation of the total extracts which, when all is said, remains the best practical method of using these products consists generally in the desiccation of the organ previously crushed or made into a pulp. This desiccation is done in a vacuum at a low temperature and is a rather delicate procedure, considering how easily the organs are affected. It must be carried out very rapidly and Chamagne has shown that the toxicity of these products increases in proportion with the time it takes to prepare them. Certain manufacturers add a slight quantity of antiseptic substances to assure proper keeping. These products are usually prepared as powders in forms of compressed tablets or in gelatine capsules.

Next to these dried extracts and certain liquid preparations, such as the blood of animals having had their thyroid removed, we must also mention glycerin extracts of these substances which occasionally give excellent results. In this way bone marrow, liver extract, etc., are prepared. The preparation is made by macerating the organ in glycerin. These same procedures have been employed with alcohol, with oils and with ether, but they are rarely used. Ether, however, extracts certain liquids which might be of value in certain cases. (Iscovesco).

THE ADMINISTRATION OF ORGANO THERAPEUTIC PRODUCTS.

From what we have just said, we see that the most common method of administration will be by mouth.

These products can be administered diluted in fluids or food; it is, however, essential that the temperature be below 50 degrees C. This method of administration is particularly useful in children.

In the past it was believed that these products could be administered by hypodermic injections. It was thus that Brown-Sequard tried his first therapeutic experiments, notably the use of testicular extract. We know now that this mode of administration has no particular advantage.

We have already said that the digestive juices do not destroy the extracts and they still keep all their properties. Perhaps hypodermic administration would give more rapid results, but organo therapy has never been a treatment which was very urgent. It is also possible that the subcutaneous administration would cause the formation of antigen which possibly might cause the appearance of anaphylactic phenomena.

The administration by injection is limited to serums previously made aseptic. These can be given either intramuscularly or intravenously; this last way of administering it is, however, contraindicated in extracts of organs liable to cause massive coagulation and for this reason would be extremely dangerous.

In certain patients, particularly hard to treat, extracts of organs can be administered by the rectal route. In this method macerations of organs are given, the rectum having previously been washed out with an enema, and the patient being given with the injection a small quantity of laudanum and kept in bed.

GENERAL INDICATIONS FOR ORGANO THERAPY.

The general indications for organo therapy result directly of what we have said of the modes of actions exerted by the various products which are utilized. The object, in the majority of cases, is to supplement or stimulate an organ whose function is impaired. Every time that an organ is functionating deficiently, the indication is to administer the extracts of a corresponding organ. Partly to give to the organism the secretions which it is missing and partly to stimulate the function of the deficient organ.

Glandular synergy by means of which certain organs supplement each other, allows us sometimes to substitute the extract of one organ for another. Just as we know that the ingestion of an extract is susceptible to stimulate the function of an organ other than the one it has been extracted from. These facts are well worth remembering when it comes to understand certain indications or explain certain effects.

As regards certain particular qualities which are utilized in the treatment of certain symptoms without any pathological relation to the organ from which the extract is obtained, (suprarenalin to contract the blood-vessels, for instance) there is no general rule for these.

CONTRAINDICATION TO ORGANO THERAPY.

There does not seem to be any general contraindication to the use of the organo therapy and it does not prevent the use of any other therapeutic method.

This results in organo therapy being very convenient to employ and, furthermore, it is nearly always without danger and this is easy to understand when we remember that nothing foreign is introduced into the organism.

The danger of possible anaphylaxis has been mentioned by some. It seems that this theory has been abused of, and when this phenomenon is suggested as occurring after the oral administration of extracts of organs it seems to be going too far.

There are, however, a certain number of facts which we must keep in mind when we administer this type of medication. The first one is that a few of these products have a fairly high toxicity. Carnot drew attention to the toxicity of bile which cannot be administered without a certain amount of caution. Suprarenalin and thyroid also require a certain amount of supervision. In spite of it all, the toxicity of thyroid has been greatly exaggerated. As regards suprarenalin (next to which we must place pituitrin) it is only toxic when injected. Suprarenalin and pituitrin can be given by mouth in large doses without any danger.

If organo therapy in general has no contraindications, it is perfectly evident that each individual product has contraindications which result from some of its actions and is, therefore, closely allied to the condition of the patient at the time. To administer thyroid extract in therapeutic doses to a normal individual with a normally functionating thyroid does not cause much inconvenience; to give him large doses might result in bringing on a condition of hyperthyroidism in the patient. We must also note the contraindication of thyroid in patients with heart disease.

TECHNIQUE OF ORGANO THERAPY.

The choice of the product to be utilized, depends on the general rules we have mentioned. It also depends on the special indications which we learn from the study of diseases to which organo therapy can be applied. The ease of administration and the harmlessness of organo therapy, as well as the uncertain knowledge we still have of the subject, allow us to experiment rather extensively, remembering, however, the special contraindications for each product. In certain cases we have to resort to complex organo therapy. In these cases complex physiological and pathological syndromes call for complex organo therapy.

There are certain organs whose internal secretions are closely connected. For instance, the internal secretion of the duodenum (secretin) acts on the secretion of pancreatic juice, and this juice, once secreted, finds in the secretions of the intestines its activator (enterokinase). A mixture of duodenal extract and of pancreatic extract is, therefore, a rational procedure.

We have previously referred to associated insufficiencies of several organs, particularly of several endocrine glands. In these cases, it is perfectly legitimate to use several extracts. It is possible to obtain preparations of different extracts in the proportions in which they are best given. It is also possible to alternate in giving various extracts, for these substances act very slowly. It has also the advantage of modifying each product as the case is being treated according to the results.

Sometimes it may be indicated to give two products having an opposite action. Supposing we administer pituitrin; this might cause hypofunction of a diseased thyroid. In these cases, it may be necessary to administer at the same time thyroid extract to prevent this.

DOSES OF ORGANO THERAPEUTIC PRODUCTS.

We are not going to give here the dose of each extract. We are simply stating a few general principles.

We have found that it is not necessary to divide our doses into several portions each day. The action of these products being very slow, it is not necessary to give small repeated doses.

We have already pointed out that these products, outside of a few preparations, are very easy to handle and for this reason, doses can be varied according to the condition of the patient and the results obtained.

Physicians should remember that it takes a long time for results to be noticed; sometimes weeks go by before any appreciable changes occur. This is said in order to avoid the possible error of increasing the dose too rapidly because of its apparent inefficacy.

Children have a high tolerance for these products. As a rule, the dose for a child 2½ is about ¼ of the adult dose, that of a child 5—⅓; of 10—½. From 15 on, the dose is that of an adult. (Hallion).

CERTAIN GENERALITIES ON THE CHIEF ORGANO THERAPEUTIC PRODUCTS.

We will now go over very rapidly the chief organo therapeutic products. As it will be seen, the therapeutic indications are usually the same as those relating to the physiology of the organ.

Biliary Organo Therapy.—Bile acts in the intestines as a regenerator of the mucosa and a stimulant of intestinal peristalsis. It helps in the assimilation of fats and has an antiseptic action. It can, to a certain extent, supplement a decrease in the secretion of bile and is the best biliary stimulant as well as the best cholagogue.

Fresh bile is used in enemata or as a dry bile extract. The indications are: constipation, muco membranous entero colitis, gall stones, intestinal fermentation, etc. The extract of bile has been advocated in pulmonary tuberculosis (Lemoine and Gerard).

Duodenal Organo Therapy.—The duodenum has an external secretion. The duodenal secretion contains two ferments, erepsin and enterokinase. There is also an internal secretion which is secretin. This substance, at the time gastric contents enter the duodenum, stimulates the secretion of pancreatic, bile and intestinal juices. The chief action of duodenal organo therapy is to stimulate the action of secretin and re-enforce biliary, duodenal and pancreatic secretions and stimulate the contractions of the intestines.

The dried extract is used in intestinal dyspepsia, constipation and auto intoxication.

INTESTINAL ORGANO THERAPY.—This preparation is employed in the same type of conditions as the previous one.

GANGLIONAL ORGANO THERAPY.—The lymphatic ganglia play a part in the formation of the white cells of the blood which protect the organism against infection. The administration of the extract of these glands aims in increasing leukocytosis and to contribute to the general defence of the organism.

The glycerin extract of the lymph glands is used (to be injected intramuscularly) or the total extract in infectious diseases, rheumatism, glandular fever, purpural infections, etc.

GASTRIC ORGANO THERAPY.—The internal secretion of the stomach is not well known. Gastric organo therapy aims chiefly in increasing the external secretion, the gastric juice and to a certain extent makes up for a deficiency of gastric juice.

Neutralized gastric juice can be used or the dried extract of the gastric mucosa. The chief indications are in decreased gastric secretion, gastro enteritis and certain gastric neuroses.

HEMATOETHYROIDIN ORGANO THERAPY.—This consists in utilizing the blood of animals whose thyroid gland has been removed (Ballet and Enriquez). It is recommended in certain disorders due to hyperfunction of the thyroid. Moebius's serum in Germany is obtained from sheep from which the thyroid has been removed. The serum of dethyroided horses is preferable.

It is given in doses of from 3 to 5 teaspoonfuls a day. It is used in exophthalmic goitre and certain other manifestations of hyperthyroidism (insomnia, diabetes).

Hepatic Organo Therapy.—The extracts of liver contain many physiological properties. The chief aim in organo therapy is to stimulate the affected organ by means of homologous extracts. The fact that the liver activates the coagubility of the blood is also utilized in certain hemorrhagic affections (Gilbert and Carnot). As a rule extracts of liver can be utilized whenever one of the liver functions is defective. (Glycogenic, antitoxic, etc.).

Therapeutically we utilize the total dried extract or glycerin extracts or oily extracts (cod liver oil). These preparations give very good results in cirrhosis of the liver (ascites, cerebral disturbances, hemorrhages) and hemoptysis of tuberculosis, in diabetes (except diabetes due to a perihepatitis in which case this form of treatment is liable to aggravate the disease), in cancer of the liver, gout and various other conditions.

Pituitary Organo Therapy.—There is a certain degree of similarity between the extracts of this gland and of the suprarenals. Extracts of pituitary slow down and strengthen the systolic contraction of the heart and cause a marked hypertension. There is also a stimulation of the pituitary itself. There is also a stimulation of the adrenals and an inhibitive action on the thyroid. As regards its stimulating action on the heart, the blood vessels, the smooth muscles, the posterior lobe alone is effective. Nevertheless, it is best to prescribe the extract of both lobes, as organo therapy is chiefly aiming at glandular insufficiency.

The dried extract (10 to 40 centigrams daily) is given in asthenia, hypotension, chronic myocarditis, hyperthyroidism (Basedow's disease), infectious diseases (typhoid, influenza, erysipelas), and tachycardia. Pituitary extract should not be used in cases with hypertension. If we desire direct and immediate results on the circulation and not a stimulation of the pituitary, the extract of the posterior lobe is indicated.

MAMMARY ORGANO THERAPY.—This preparation has a marked effect on lactation and an indirect action on uterine affections. Mammary organo therapy seems to be antagonistic to ovarian organo therapy. (Batuaud).[1]

The dried total extract of the cow's mammary gland is used. This is an efficacious galactogogue. It is chiefly utilized to relieve the congestion of the female genital organs in fibroma, menorrhagia and metrorrhagia.

MEDULLARY ORGANO THERAPY.—Bone marrow is only active during the period of development. Therefore, red bone marrow alone should be utilized in preference to the yellow.

It can be administered fresh as a sandwich, as bone marrow jelly (Barrs), as dried extracts or glycerinated extracts. This type of medication is efficacious in anemias of childhood, in chloro anemia, in pernicious anemia (only temporary results) and leukemias. Strange to say good results have been obtained in polycythemia where the bone marrow is already hyperactive (Glaessner).

NERVOUS ORGANO THERAPY.—This is based on the lipoid and phosphorous content of the nervous system and some authorities believe that they may be an internal secretion from the nerve cells. It is obtained by means of dried or oily extracts of brain and spinal cord. It is used in epilepsy, neurasthenia and dementia precox.

ORCHITIC ORGANO THERAPY.—This was the first one used (Brown-Sequard) and was based on the external (spermatozoon) and internal secretion of the testicle.

---

[1] Clinically mammary extract is not an efficient galactogogue. So far as I know none of the gland extracts has proved beneficial.

Mammary extract seems to have a direct action on uterine musculature. Its best effects are seen in subinvolution and its complications.

The latter is not yet well understood as to its physiological effects.

Dried or oily or glycerin extracts may be used. This preparation was considered of value in temporary impotence, in neurasthenia, senility and chlorosis of young girls. At the present time there is considerable doubt as to its efficacy.

Ovarian Organo Therapy.—The ovary has two functions; one represented by laying eggs, the other an internal secretion, which is largely due to corpus luteum, but to a certain extent also by the interstitial part of the ovary. This internal secretion acts chiefly upon menstruation, and some of the phenomena at the beginning of pregnancy, on the nutrition and development of the pelvic organs and the development of the breasts. The extract of the ovary in general causes stimulation and congestion of the female genital organs and in this manner is antagonistic to mammary extracts.

In organo therapy, this preparation is usually given in tablets of the dried extract (25 to 50 centigrams) daily. Sometimes it is given as a glycerin extract hypodermically. The chief indications are those of ovarian insufficiency, notably in women whose ovaries have been removed in disturbances of the menopause and puberty. (Insufficient menses, syndrome of adiposis genitalis of young girls), in psychosis of genital origin, Dercum's disease, certain cases of Basedow's disease and obstinate vomiting of pregnancy.

Pancreatic Organo Therapy.—The pancreas has an external secretion (pancreatic juice) and an internal secretion whose function is to moderate the formation of sugar by the liver. The chief function of pancreatic extracts is to stimulate the function of the pancreas.

They can also, to a certain extent, supplement directly the deficiency of both pancreatic secretions.

In organo therapy the total dried extracts of the gland are used. The indications are: chronic pancreatitis, diarrhea associated with remains of muscles, fibres and fats (pancreatic insufficiency), intolerance to milk, pancreatic diabetes, intestinal dyspepsia.

We have already shown why it seemed rational to combine pancreatic extract with duodenal extract.

PARATHYROID ORGANO THERAPY.—Insufficiency of the parathyroids is liable to produce in man attacks of tetany, convulsions or eclampsia. The total dried extract has been advocated in these conditions as well as in paralysis agitans.

PLACENTARY ORGANO THERAPY.—The placenta secretes ferments and other substances which act on the uterus and the other genital organs.

In organo therapy the dried extract of sheep's placenta is utilized in large doses. It is a galactogogue For the same reason the placenta from the patient herself may be used (Bouchacourt), but this is usually repugnant to the patient.

PROSTATIC ORGANO THERAPY.—There is a double secretion of the prostate, one internal, the other external. A deficiency of these secretions is liable to result in sterility or nervous disorders (Beard considers that neurasthenia is very often caused by prostatic affections). It is mainly in neurasthenia that dried prostatic extracts give appreciable results.

PULMONARY ORGANO THERAPY.—The internal secretion of the lung is not very well known. The extract of the lung (dried or glycerinated) has been utilized with some degree of success in purulent pleurisy with vomiting, and some very good results have also been obtained in pulmonary tuberculosis.

Renal Organo Therapy.—The kidney has two secretions: one external, which is the urine, the other internal, which seems to act mainly as an antitoxic substance.

Maceration of the kidney and serum from the renal veins, as well as peptic extract (Gilbert and Castaigne) and glycerinated extract are used. Renal organo therapy has given the best results in the acute symptoms of uremia and in eclampsia of pregnancy. In acute nephritis, complete cures have resulted. This type of medication is contraindicated when there is a decrease of elimination of urine after the first dose.

Blood Organo Therapy.—The best example of this is blood transfusion which does not belong to the present subject. Preparations of blood or of hemoglobin are still utilized and still preserve, in spite of the digestive juices certain physiological effects. In therapeutics, however, blood serum is the preparation most commonly employed.

The serum is employed either liquid or dried, by mouth or by injection (serum of normal animals). It is used in infections to stimulate phagocytosis, in hemophilia and as a stimulant of nutrition in general. In anemias, normal serum may be used or serums of animals which have been bled repeatedly and are, therefore, in a state of regeneration. (Carnot).

Splenic Organo Therapy.—This aims chiefly to stimulate the normal functions of the spleen, that is, lymph and blood forming. This type of organo therapy seems to have also some effect on deficient bone marrow.

Fresh spleen is used very occasionally; as a rule as a dried total extract; or a glycerinated extract is best. It is used in malaria, anemias, hemorrhages and tuberculosis.

SUPRARENAL ORGANO THERAPY.—The extract of the suprarenal glands or synthetic suprarenalin (the only organo therapeutic substance which has ever been made) has a cardio vascular action which manifests itself by a rise in blood pressure, increase in the contractions of the heart and slowing of the pulse. It also causes contraction of nearly all the smooth muscles.

It has an antitoxic action, an action of the glycogenic function and on various glandular secretions. From this it is easy to understand why suprarenal insufficiency manifests itself by many complex symptoms, the chief ones of which are: hypotension, anorexia, vomiting, asthenia, sudden death often terminating the disease. A suprarenal organo therapy is indicated in deficiency of that organ. Except in cases where we wish to get the local effect of suprarenalin, it is best given as a dried extract or glycerinated extract. As a rule the dose is between 40 and 60 centigrams daily.

THYMIC ORGANO THERAPY.—The extracts of the thymus are supposed to have some effect on the development of children.

Fresh thymus, dried thymus, etc., are advocated in rickets, congenital debility and athrepsia.

THYROID ORGANO THERAPY.—It is possible to stimulate a defective thyroid or to substitute for the absence of some of the thyroid secretions. The secretions of the thyroid have a marked effect on some of the vital phenomena; acceleration of the heart, stimulation of the formation of blood, diuretic action, etc. There is also an anti-toxic action. In reality, nearly all the body functions are affected.

It results from this that the indications for thyroid medication are multiple. The chief indications are: myxedema, lymphatism, simple obesity, nervous exhaustion (Fiessinger), Dercum's disease, chronic rheumatism, certain migraines (Leopold Levi), slowness in repair of fractures, certain dermatoses and infections.

The fresh gland can be used (rarely now), total dried extract, and glycerinated extracts (rarely used). It must be used very carefully in individuals with cardiac disease and is contraindicated in hyperthyroidism and notably, in spite of a few exceptions, in Basedow's disease.

INDEX

A

Abdominal sympathetic syndrome, 337
Acute thyroiditis, 97
Acromegalia, 172
Acroparesthesia, 228
Addisonism, 148
Addison's disease, 143, 326
Adrenal debility, 153
Adrenal encephalopathy, 136
Adrenal gland, 130
Adrenal glycosuria, 316
Adrenal sympathetic syndrome, 337
Adrenal vascular syndrome, 159
Adrenal white line, 132
Anatomy of the parasympathetic, 286, 292, 300, 301
Anatomy of the sympathetic system, 286, 300
Angina pectoris, 322
Aplasia of the thymus, 120, 126
Asthma, 322
Atropin, 320
Autonomic systems, See local visceral systems.

B

Basedow's disease, 75, 85, 324
Bichat, 255, 261
Blandin, 261
Bulbo spinal myasthenia, 250

C

Castration, 210, 212, 223
Cells of Stilling Clarke, 278, 279
Centres of the sympathetic system, 274, 281
Cerebral trunk, 275
Cervical sympathetic syndrome, 328
Chromaffin, 311
Claude Bernard, 262
Coelialgia, 339
Column of Stilling Clarke, 273
Congenital thymic iodiocy, 127
Corpus luteum, 222
Cranial parasympathetic, 287, 291
Cretinism, 67
Cryptorchidism, See undescended testicles.

D

Dercum's disease, 228
Diabetes insipidus, 190, 203
Dorsal lumbar vegetative system, 307

E

Elective pharmacological action, 306
Emotions, 28, 320
Endocrine and sympathetic syndromes, 293
Endocrine glands, 4, 25
Endocrine heredity, 27
Endocrine sympathetic syndromes, 324
Endocrine tests, 35
Enteralgic crisis, 346
Enterokinase, 365
Epiphysis, See pineal glands
Eppiner and Hess, 315, 317, 320, 324
Erepsin, 365
Erector plexus, 280
Erythromelalgia, 347
Eukinase, 365
Eunuchism, 212
Exophthalmos, 78, 332
Extract of bile, 365
Extract of bone marrow, 368
Extract of brain, 368
Extract of duodenum, 365
Extract of ganglia, 366
Extract of gastric mucosa, 366
Extract of intestines, 366
Extract of liver, 367
Extract of mammary gland, 236, 368
Extract of ovary, 232, 369
Extract of pancreas, 369
Extract of parathyroid, 95, 370
Extract of pituitary, 367

Extract of placenta, 370
Extract of prostate, 370
Extract of pulmonary tissue, 370
Extract of spleen, 371
Extract of suprarenals, 142, 372
Extract of testicles, 178, 208, 220, 368
Extract of thymus, 372
Extract of thyroid, 51, 72, 372

F

Facial hemiatrophy, 334
Feminism, 216, 249
Fibres of Remak, 263
Functions of the adrenals, 128
Functions of the ovaries, 221
Functions of the parathyroids, 102
Functions of the pituitary, 170
Functions of the testicles, 208
Functions of the thymus, 117
Functions of the thyroid, 57
Functional vegetative arc 264
Frolich's syndrome, 185

G

Ganglia, 267, 281
Ganglionic chain, See ganglia.
Gaskell, 262, 299
Gastric crisis, 340, 345
Gastro intestinal neurosis, 322
General anatomy of the sympathetic, 268, 272
Gerodermia genito dystrophy, 214
Gigantism, 178
Gigantism of breast, 240
Glandular hyperfunction, 16

H

Harmazones, 14
Heart, 301
Hemato ethyroidin, 366
Hemapoic serum, 371
Hemorrhages of the adrenals, 140
Hyperadrenalism, 156
Hyperfunction of the ovaries, 233
Hyperorchidia, 218
Hyperthyroidism, 59, 75, 79
Hypertrophy of the thymus, 120, 126
Hypothyroidism, See insufficiency of the thyroid.

I

Infantilism 68, 184, 215, 228, 249
Insufficiency of the adrenals, 132, 137, 152
Insufficiency of the endocrine glands, 16
Insufficiency of the ovaries 191, 223, 228
Insufficiency of the parathyroids, 103
Insufficiency of the testicles, 215
Insufficiency of the thyroid, 60, 67, 230
Internal secretions and the vegetative system, 310, 311, 312
Interstitial gland, 209, 221
Intestinal cancer, 341
Intestinal affections, 341
Iodothyrin, 359

J

Johnstone, 255
Juvenilism, 216

L

Langley, 262
Local and visceral system, 287, 301
Local and visceral tonus, 309
Lucas, 255

M

Macrogenito somatism, 202
Mammary gland, 238
Mammary gland hypertrophy, 239, 241
Mediastinal sympathetic syndrome, 335
Melanodermia, 144, 145, 147
Menopause, 227
Mesenteric neuralgia, 344
Metrorrhagia, 234
Migraine, 227
Motor organic vegetative arc, 264
Muco membranous entero colitis, 346
Mueller, 262
Myxedema, 60
Motor nuclei, 264

N

Neurothrophic substances, 310, 311
Normal blood serum, 371
Nuclei of Stilling Clarke, 278

O

Obesity, 68, 86, 225, 328
Ocular sympathetic syndrome, 328
Oculo cardiac reflex, 317
Organo therapy, 47, 52
Organo therapy using adrenal extract, 142
Organo therapy using mammary extract, 236
Organo therapy using ovarian extract, 232
Organo therapy using parathyroid extract, 114
Organo therapy using pituitary extract, 367.
Organo therapy using testicular extract, 220
Organo therapy using thyroid extract, 72
Ovarian crisis, 322
Ovarian function, See functions of ovaries.
Ovarian graft, 231
Ovarian spots, 228
Organo vegetative cells, 263
Organo vegetative centres, 274, 275, 277, 278
Organo vegetative sensory centres, 278

P

Pachydermic cachexia, 62
Pancreatin, 369
Pancreatitis, 341
Paradox of tonus, 308
Paraganglia, 311
Parasympathetic, 304
Parasympathetiocotonia, same as parasympathicotonia.
Parasympathicotonia, 315
Parathyroid function, 102
Parathyroid graft, 114
Parathyroid syndrome, 103
Pelvic parasympathetic, 300
Pelvic plexus, 281
Peripheral sympathetic syndromes, 346
Periodic hydrarthrosis, 313
Peritonitis, 340
Petit, 255
Pharmacological antagonism, 306
Pharmacological tonus, 307
Pharmacology, 306, 349
Pilocarpin, 284
Pineal gland, 201
Pineal syndrome, 201
Pituitary glycosuria, 188
Pituitary polyuria, 190
Pituitary syndromes, 172
Pituitary tumor, 162
Plexus, 283
Pluriglandular syndromes, 243
Pneumogastric, See vagus.
Post ganglionic fibres, 265
Preganglionic fibres, 265
Progreria, 168
Pseudo hermaphroidism, 163
Pseudo peritonitis, 136

R

Raynaud's disease, 347
Rectal crisis, 322

S

Sclerodermia, 327
Sea sickness, 321
Secretin, 365
Senile dwarfism, 168
Sensory vegetative centres, 278
Sensory vegetative tracts, 270, 274
Sergent's line, 132
Serum of Moebius, 366
Shock, 321
Skotzis, 212, 214
Solar sympathetic syndrome, 337
Sudden death due to adrenal insufficiency 136
Sudden death due to parathyroid insufficiency, 116
Sudden death of thymic origin, 123
Suprarenalin, 129, 144, 151, 316, 372
Sympathetic, 22, 254, 304
Sympatheticotonia, See sympathicotonia.
Sympathicotonia, 315
Syndrome of Addisonism, 143, 149
Syndrome of adiposo genitalis, 185
Syndrome of adrenal origin, 132
Syndrome of Basedow's disease, 89

T

Tabes, 322
Tetany, 103
Testicular crisis, 322
Thyroglobulin, 57
Thyroid atrophy, 62
Thyroid function, 57
Thyroid graft, 71
Thyroid instability, 96
Tonus, 308, 309
Trophic edema, 347
Tuberculosis of the thyroid, 97
Tuberculosis of the adrenals, 143, 148
Tumor of the pituitary, 192

U

Undescended testicles, 209, 214

V

Vagotonia, 314, 315, 318
Vagus nerve, 279, 281
Vegetative system, 254
Virilism, 164, 205

W

Winslow 255, 262
Wrisberg 284, 291, 303

X

X-ray, 45, 210, 222

LANE MEDICAL LIBRARY

To avoid fine, this book should be returned on
or before the date last stamped below.

NOV 1 '22
JAN 10 '23
Oct. 12, 19
MAY 6 -
AUG 25 '24
JAN 12 '25
JAN 12 '25
JUL [illegible] '25
DEC 16 '25
JUN -4 '26

APR 23 192[illegible]
SEP [illegible]
OCT -1 1930
OCT 31 1930
NOV 11 1931
~~[illegible]~~
MAR 31 1933
June 3
MAR 31 1936

L648 Lereboullet, P. 53051
L61m Endocrine glands
1922

NAME	DATE DUE
P Triggs	APR -1 1938 Mar 1
B. Slaughter	Jan [illegible]
(nurse)	
[illegible]	MAR 21